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Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and-Dibenzofurans (CDDs and CDFs) and 1989 Update

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16. ABSTRACT

In 1987, the U.S. Environmental Protection Agency (EPA) formally adopted an interim toxicity equivalency factor (TEF) procedure (EPA-TEF/87), which has been used by EPA in addressing a variety of situations of environmental contamination involving CDDs and CDFs. The EPA-TEF/87 method, published as "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and -Dibenzofurans (CDDs and CDFs)," is republished as Part I of this document.

Since the time that the 1987 report was published, the EPA has been active in an international project aimed at adopting a common set of TEFs, the International TEFs/89 (I-TEFs/89), to promote consistency in addressing contamination involving CDDs and CDFs. The "1989 Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and -Dibenzofurans (CDDs and CDFs)" identifies EPA's adoption of the I-TEFs/89 as a revision to the EPA-TEFs/87 currently in use. The 1989 Update is Part II of this document.

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EPA

Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-Dioxins and -Dibenzofurans (CDDs and CDFs) and 1989 Update

RISK ASSESSMENT FORUM

REPRODUCED BY
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Notice

The toxicity equivalency factor (TEF) method is an interim procedure for assessing the risks associated with exposures to complex mixtures of chlorinated dibenzo-*p*-dioxins and dibenzofurans (CDDs and CDFs). The method relates the toxicity of the 210 structurally related chemical pollutants and is based on a limited data base of *in vivo* and *in vitro* toxicity testing. By relating the toxicity of the 209 CDDs and CDFs to the highly studied 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), the approach simplifies the assessment of risks involving exposures to mixtures of CDDs and CDFs, such as incinerator fly ash, hazardous wastes, contaminated soils, and biological media. During the late 1970s and early 1980s, various regulatory agencies in the United States, Canada, and Europe, developed their own TEF schemes. As a result, numerous and slightly different TEF methods existed which complicated communication among scientists and agencies in addressing the toxicological significance of complex mixtures of CDDs and CDFs.

Part I

In 1987, the EPA formally adopted an interim TEF procedure (EPA-TEF/87), which has been used by EPA regulatory programs and Regions in addressing a variety of situations of environmental contamination involving CDDs and CDFs. The EPA-TEF/87 method, published as "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-dioxins and -Dibenzofurans (CDDs and CDFs)", (EPA/625/3-87/012) is republished (with minor editorial corrections) in this updated report. In the 1987 report, the Agency emphasized that the method was interim in nature and committed itself to periodically update the TEFs as additional toxicity data were generated.

Part II

Since the time that the 1987 report was published, the Agency was active in an international project aimed at adopting a common set of TEFs, the International TEFs/89 (I-TEFs/89), to promote consistency in addressing contamination involving CDDs and CDFs. This first update report, "1989 Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-Dioxins and -Dibenzofurans (CDDs and CDFs)," identifies EPA's adoption of the I-TEFs/89 as a revision to the EPA-TEFs/87 currently in use. In general, the effect of these modifications is likely to be modest for many complex mixtures. This report also presents the rationale, methodology, and toxicity data used to determine the new values and describes the differences between the two schemes. The I-TEFs/89 represent an improvement in an already useful risk assessment tool. However, the approach remains interim in nature and should be continued to be revised as new data are developed. In addition, the complete replacement of any TEF method by a bioassay method appears to be feasible within the near future.

In the 1987 report, the term toxicity "equivalence" factor was used, but for the 1989 update, the term toxicity "equivalency" factor is being used to be consistent with NATO/CCMS.

Part I

Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-Dioxins and -Dibenzofurans (CDDs and CDFs)

October 1986

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Preface

As part of its effort to address risks posed by chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans (CDDs and CDFs) in the environment, the U.S. Environmental Protection Agency (EPA) has adopted an interim procedure, based on dioxin "toxicity equivalence" factors (TEFs), for estimating the hazard and dose-response of complex mixtures containing CDDs and CDFs in addition to 2,3,7,8-TCDD. The TEF procedure, and the scientific data upon which it is based, are the subject of this report.

This report, which has been extensively reviewed by EPA and external (non-EPA) experts, was prepared for EPA's Risk Assessment Forum (Forum) and was approved by the EPA Risk Assessment Council in August 1986. In September 1986, the report was reviewed by a special Subcommittee of the Agency's Science Advisory Board (SAB), a congressionally mandated body of independent scientists.

The SAB Subcommittee concurred with EPA's view that the TEF method is a reasonable interim approach to assessing the health risks associated with exposure to mixtures of CDDs and CDFs for risk management purposes. They noted that the method proposed may lack scientific validity and agreed with EPA on the importance of efforts to validate the method by selected experimental testing of hypotheses. The Agency received strong encouragement to continue research on other approaches to estimating risks for substances in mixtures. The Subcommittee also indicated that it was important that the interim approach be re-evaluated systematically by EPA as lessons are learned from toxicological research and from application. Lastly, the group cautioned that the interim TEF method should be largely reserved for special situations where the components of the mixture are known, where the composition of the mixture is not expected to vary much with time, and where the extrapolations are consistent with existing animal data. Some aspects of the report have been revised to take the Subcommittee's comments into account.

These SAB comments reinforce EPA's views on the strengths and limitations of the TEF approach. Throughout development of the report, EPA scientists have emphasized that the TEF approach is an interim science policy to be used pending development of more rigorous and scientifically robust approaches, some of which are mentioned in the report. The Agency intends to encourage and to pursue a range of research activities which will both further test the hypotheses that underlie this interim procedure and lead to alternative, more direct approaches to determining the toxicity of CDD and CDF mixtures.

Research on CDDs and CDFs continues at a rapid pace, and the Agency is closely monitoring changes in the data base upon which the TEF approach has been established. Through an annual updating of the approach, the Forum will assure that TEF factors remain current with the existing animal data.

The TEF procedure will be used generally throughout the Agency for situations in which the components of the mixture are known (or can be reasonably anticipated) and where the composition is not expected to vary greatly with time.

On other issues the SAB Subcommittee and other peer reviewers recommended that EPA consider more explicitly the effects of pharmacodynamics (the bioavailability, absorption, distribution, metabolism, and elimination) of relevant environmental mixtures in whole animals when assigning TEFs to the homologues and isomers of CDDs and CDFs. For example, studies suggest that higher chlorinated CDDs and CDFs are less likely to be absorbed during acute exposures. Further, some CDDs and CDFs are more likely to be metabolized and eliminated than are others. The Forum will review these issues and recommend changes in some TEFs, as approporiate.

In summary, the TEF approach provides a useful interim method for consistently interpreting the significance of CDD and CDF residues in the environment, until more direct methods are available. Users should be aware of the uncertainties associated with the procedure. In addition to the uncertainties inherent in the 2,3,7,8-TCDD quantitative risk assessment, which the TEF approach implicitly adopts, the approach includes the added qualitative assumption that the other CDDs and CDFs will demonstrate the same chronic effects as 2,3,7,8-TCDD. While there are good scientific reasons to expect this to be the case, the data to support this assumption are limited.

The Agency plans to update the TEFs on a regular basis, incorporating additional information as it becomes available so that the approach will reflect the best current scientific thinking. The intent is to replace this interim procedure with a more rigorous approach as research results permit.

I. Summary

The U.S. Environmental Protection Agency (EPA) is often confronted with the need to determine the risks associated with exposure to materials such as soot, incinerator fly ash, industrial wastes, and soils which contain complex mixtures of chlorinated dibenzo-*p*-dioxins (CDDs) and chlorinated dibenzofurans (CDFs).[1] Recognizing the public and toxicological concern generated by these chemicals and the significant gaps in our ability to evaluate the human health potential of these compounds by existing procedures, the CDD/CDF Technical Panel of the Risk Assessment Forum (Forum) is recommending an interim method to aid in the assessment of the human health risks posed by mixtures of CDDs and CDFs until data gaps are filled.

The Technical Panel has reviewed a spectrum of approaches for making such assessments, consistent with EPA's Guidelines for the Health Risk Assessment of Chemical Mixtures, and has concluded that a direct biological assessment of the toxicity of complex mixtures of CDDs and CDFs is preferred. However, a validated bioassay that can plausibly be applied to such mixtures is not now available, although promising research is in progress in the area. An alternative approach involves explicit analysis and toxicological determination of each of the constituent CDD/CDF congeners. The data required for such an approach also need to be developed and are not likely to be generated soon. The Forum therefore concludes that, as an interim science policy measure, a reasonable estimate of the toxic risks associated with a mixture of CDDs and CDFs can be made by taking into account the distribution of CDD/CDF congeners or homologues and the likely relative toxicity of these compounds. This document describes the recommended interim procedure for generating the "2378-TCDD equivalence" of complex mixtures of CDDs and CDFs, based on congener- or homologue-specific data, and for using such information in assessing risk. (The recommendations are summarized in the rightmost column of Table 1.)

The Forum acknowledges that this procedure is not based on a thoroughly established scientific foundation. Instead, the approach represents a consensus recommendation for interim science policy, subject to change as additional data are available. The approach is judged to be applicable to mixtures of CDDs and CDFs, but should not be construed as being applicable as well to mixtures of other chemicals.

The basis of this approach, i.e., the assignment of toxicity equivalence factors (TEFs) is subject to revision as new scientific data become available in the future. Consequently, risk assessors and risk managers are urged to use informed discretion, noting specific problems on a case-by-case basis, when applying the procedure to any particular situation. The Forum urges the support of research to test further the hypotheses that underlie this interim procedure and to develop the preferred approaches.

[1] See Appendix A for the nomenclature and conventions used in this paper.

Table 1. Some Approaches to Estimating Relative Toxicities of PCDDs and PCDFs

Basis: compound	Swiss[a]	Grant[b] Olie[c] Commoner[d]	New York State[e]	Ontario[f]	FDA[g]	CA[h]	EPA[i] 1981	EPA current recommend.
(Basis)	Enzyme		LD_{50}	Various effects	Various effects			Various effects
Mono thru di CDDs	0	0	0	0	0	0	0	0
Tri CDDs	0	0	0	1	0	0	0	0
2378-TCDD	1	1	1	1	1	1	1	1
other TCDDs	0.01	1	0	0.01	0	0	1	0.01
2378-PeCDDs	0.1	0.1	1	1	0	1	0	0.5
other PeCDDs	0.1	0.1	0	0.01	0	0	0	0.005
2378-HxCDDs	0.1	0.1	0.03	1	0.02	1	0	0.04
other HxCDDs	0.1	0.1	0	0.01	0.02	0	0	0.0004
2378-HpCDDs	0.01	0.1	0	1	0.005	1	0	0.001
other HpCDDs	0.01	0.1	0	0.01	0.005	0	0	0.00001
OCDD	0	0	0	0	<0.00001	1	0	0
2378-TCDFs	0.1	0.1	0.33	0.02	0	1	0	0.1
other TCDFs	0.1	0.1	0	0.0002	0	0	0	0.001
2378-PeCDFs	0.1	0.1	0.33	0.02	0	1	0	0.1
other PeCDFs	0.1	0.1	0	0.0002	0	0	0	0.001

Table 1. (continued)

Basis/ compound	Swiss[a]	Grant[b] Olie[c] Commoner[d]	New York State[e]	Ontario[f]	FDA[g]	CA[h]	EPA[i] 1981	EPA current recommend.
(Basis)	Enzyme		LD_{50}	Various effects	Various effects			Various effects
2378-HxCDFs	0.1	0.1	0.01	0.02	0	1	0	0.01
other HxCDFs	0.1	0.1	0	0.0002	0	0	0	0.0001
2378-HpCDFs	0.1	0.1	0	0.02	0	1	0	0.001
other HpCDFs	0	0.1	0	0.0002	0	0	0	0.00001
OCDF	0	0	0	0	0	0	0	0

[a]Swiss government, 1982.
[b]Grant, 1977.
[c]Olie et al., 1983.
[d]Commoner et al., 1984.
[e]Eadon et al., 1982.
[f]Ontario government, 1982.
[g]U.S. DHHS, 1983.
[h]Gravitz et al., 1983.
[i]U.S. EPA, 1981

II. The Need for a Procedure for Assessing the Risk Associated with Exposure to Complex Mixtures of CDDs and CDFs

During the late 1970s, the Agency was faced with assessing the human health significance of exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD). In preparation for the cancellation hearings for the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and Silvex, the Agency generated risk assessments for several toxic responses for 2,3,7,8-TCDD. The quantitative cancer risk assessment developed by the Carcinogen Assessment Group was later adapted for use in the Water Quality Criteria (WQC) Document for 2,3,7,8-TCDD (U.S. EPA, 1984a). In addition to carcinogenicity concerns, the WQC document contains an assessment of systemic toxicity based on reproductive effects resulting from exposure to 2,3,7,8-TCDD.

Later, it became clear that exposure situations exist in the country which involve more than 2,3,7,8-TCDD alone. Data on emissions from combustion sources (e.g., hazardous waste and municipal waste incinerators) and contents of waste from certain industrial production processes indicate that the majority of the 75 CDDs and 135 CDFs can be detected in the environment.

In recent years, the reporting of at least homologue-specific data for the CDDs and CDFs has become commonplace, and the Agency has taken some steps to address the significance of these findings. For example, the Health Assessment Document for Polychlorinated Dibenzo-*p*-Dioxins, prepared for the Office of Air Quality Planning and Standards (U.S. EPA, 1985b), contains a quantitative risk assessment for a mixture of hexachlorodibenzo-*p*-dioxins (HxCDDs) based on carcinogenicity studies conducted by the National Cancer Institute. These concerns have also led to regulatory action; e.g., several industrial wastes containing tetra-, penta-, and hexa-chlorodioxins, and -dibenzofurans were recently designated by the Agency as EPA hazardous wastes.

Faced with increasing amounts of isomer- and homologue-specific data, and recognizing the significant potency and structure-activity relationships exhibited in *in vivo* and *in vitro* studies of CDDs and CDFs, the Technical Panel perceives a need to address more generally the potential risks posed by the congeners other than 2,3,7,8-TCDD and the mixture of HxCDDs.[2] Detailed consideration of the toxicity of the vast majority of the CDDs and CDFs is limited by the lack of a complete toxicological data base on most of the congeners. Further, it is unlikely that many long-term test results will be available soon. For example, research on 2,3,7,8-TCDD has been under way for more than two decades at an estimated cost of more than one hundred million dollars. Although this chemical has been investigated to a much greater extent than any of the other CDDs and CDFs, unanswered questions

[2] In the early 1980s, the Agency developed a method for an approximate assessment of the risks of the emission of CDDs and CDFs associated with the high-temperature incineration of PCBs and combustion of municipal waste (U.S. EPA, 1981; U.S. EPA, 1982); see Table 1. The procedure presented in this document is a refinement of that approach. A comparison of a variety of methods is included in Appendix B.

remain. Therefore, the Forum believes that an interim science policy position should be adopted for use in assessing risks associated with CDD/CDF mixtures, until more definitive scientific data are available.

III. Approaches to Hazard Assessment for CDD/CDF Mixtures

A. The Ideal Approach—Long-Term, Whole-Animal Toxicity Assay of Mixtures

Under ideal conditions, an assessment of the toxicity of a mixture of chemicals is best accomplished by direct evaluation of its toxic effects, e.g., by determining the effects of chronic exposure in an experimental animal (U.S. EPA, 1985a). Such an assessment is time-consuming and costly and would theoretically have to be performed for each of the many mixtures of environmental importance. Therefore, this idealized approach would cause unacceptable delays in addressing the potential health risks associated with exposures to CDD/CDF mixtures.

Long-term animal studies might be considered for some categories of CDD/CDF sources which have characteristic compositions; e.g., emission from some combustion sources. However, the need for an interim approach would remain.

B. A Promising Approach—Short-Term, Biological Assay of Mixtures

An alternative, and perhaps more achievable, approach to hazard assessment of a mixture is a short-term assay (*in vivo* or *in vitro*) that indirectly provides a measure of the mixture's potential toxicity. In the case of mixtures containing CDDs and CDFs, short-term assays are under development that directly determine the 2,3,7,8-TCDD-like response which could be used as a *measure of the toxicity of the mixture as a whole*. Such assays take advantage of the similar toxic end points induced by CDDs and CDFs, and have been used to assess the potential health hazards of exposure to CDD/CDF-contaminated soot from PCB fires (Eadon et al., 1982; Gierthy and Crane, 1984; Gravitz et al., 1983), and for predicting the potential toxicity of incinerator fly ash (Rizzardini et al., 1983; Sawyer et al., 1983).

Although the development of such "mixture assays" is progressing rapidly (e.g., Safe et al., 1985), additional work is required to more fully validate the assay findings for specific toxic end points, especially chronic effects, and aspects of pharmacokinetics need to be considered. The Forum, recognizing the importance of short-term assays, encourages research in this area.

C. A Reductionist Approach—Additivity of Toxicity of Components

In the absence of a fully developed "mixture assay," the components in a mixture of CDDs and CDFs could theoretically be identified and quantified by analytical chemists. Then the toxicity of the mixture could be estimated by *adding the toxicity contributed by each of its components*. In the case of

most environmental mixtures, however, this method would be of limited value since congener-specific analyses for the 75 CDDs and 135 CDFs potentially present in the mixture are seldom available. In addition, there is little information available on the toxic potency of most of these congeners. Therefore, this approach is not viable at this time, nor is it likely to be feasible in the near future.

D. An Interim Approach—2378-TCDD Toxicity Equivalence Factors (TEFs)

The Forum recommends a fourth alternative for estimating the risks associated with exposure to complex mixtures of CDDs and CDFs. In this approach, as in approach C above, information is obtained on the concentrations of homologues and/or congeners present in the mixture. Then, using the available toxicological data and reasoning on the basis of structure-activity relations, the significance of the exposure to each of the components is estimated and expressed as an "equivalent amount of 2378-TCDD." Combining this information with hazard information on 2,3,7,8-TCDD, and assuming additivity of effects, the risks associated with the mixture of CDDs and CDFs can be estimated if exposure is known. Key to the approach are the 2378-TCDD Toxicity Equivalence Factors (TEFs) which are derived in Section IV.

The general approach using TEFs as outlined here is not unique; several organizations have used similar approaches (see Table 1). At one extreme, all CDDs and CDFs could be assumed to be as toxic as 2,3,7,8-TCDD (all TEFs = 1). This position is not recommended since the limited long-term data (2-year cancer bioassays) on 2,3,7,8-TCDD and a mixture of 2378-HxCCDs (and the greater body of short-term data on many CDDs and CDFs) indicate that such an assumption is overly conservative. At the other extreme one could totally ignore the presence of CDDs and CDFs other than those for which adequate long-term data are available (most TEFs = 0). This position is not recommended in light of the similar toxic properties of several of these compounds and the structure-activity relationship demonstrated for effects resulting from less than lifetime exposures.

Instead, the Forum recommends that the TEF procedure presented in Section IV be adopted as a matter of science policy on an interim basis, subject to revision as new experimental data become available. Based on the available scientific information, the Forum believes that this approach represents an appropriate means of approximating the potential risk of exposure to mixtures of CDDs and CDFs for purposes of risk management.

The approach will enable the Agency to deal with many, but not all, of its problems; e.g., assigning priority to Superfund sites, estimating the extent to which a hazardous waste site should be cleaned up, guiding decisions on which manufacturing wastes can be delisted as EPA hazardous wastes, and estimating risks associated with the emission of CDDs and CDFs from combustion sources.

The remainder of this document discusses the TEF approach in greater detail, illustrates its use in risk assessment, and identifies additional research, the results of which would provide information for adjustments to this interim approach.

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IV. The 2378-TCDD Toxicity Equivalence Factors (TEFs) Approach to Assessing the Toxicity of Complex Mixtures of CDDs and CDFs

2,3,7,8-TCDD is one of 75 CDDs. Exceptionally low doses of this compound elicit a wide range of toxic responses in many animals, e.g., adverse reproductive effects, thymic atrophy, and a "wasting syndrome" leading to death. Although the Agency prefers definitive human evidence when assessing the potential human carcinogenicity of chemicals, such data are rarely available and are lacking in the case of CDDs and CDFs. However, EPA's Carcinogen Assessment Group (CAG) has determined that, based on demonstrated effects in animals, there is sufficient evidence to regard 2,3,7,8-TCDD and a mixture of two 2378-HxCDDs as probable human carcinogens. The CAG quantitative assessment indicates that these chemicals are among the most potent animal carcinogens evaluated by the Agency to date. Limited data suggest that some of the other CDDs may have other toxic effects similar to those of 2,3,7,8-TCDD, again at very low doses.

Moreover, these toxicity concerns are not restricted to CDDs. Limited experimental data, supplemented by structure/activity relationships in *in vitro* tests that are correlated with *in vivo* toxic effects of CDFs, indicate that some of these compounds exhibit "2,3,7,8-TCDD-like" toxicity (Bandiera et al., 1984; Okey et al., 1984; Safe et al, 1985).

The biochemical mechanisms leading to the toxic response resulting from exposure to CDDs and CDFs are not known in detail. However, experimental data have accumulated which suggest that an important role in the development of systemic toxicity resulting from exposure to these chemicals is played by an intracellular protein, the Ah receptor, the putative product of a gene locus designated Ah. This receptor binds halogenated polycyclic aromatic molecules, including CDDs and CDFs. It has been postulated that the Ah locus controls several pleiotropic responses: a limited, but widely expressed gene complex that includes the structural genes for aryl hydrocarbon hydroxylase (AHH) expression, and, in a few organs, such as skin and thymus, a second gene complex regulating cell proliferation and differentiation (Knutson and Poland, 1980; Neal et al., 1982; Greenlee et al., 1985a).

In several mouse strains, the expression of toxicity of 2,3,7,8-TCDD-related compounds, including cleft palate formation, liver damage, effects on body weight gain, thymic involution, and chloracnegenic response, has been correlated with their binding affinity for the Ah receptor, and with their ability to induce several enzyme systems, some of which have been linked to the expression of carcinogenicity (Poland and Knutson, 1982; Bandiera et al.,1984; Madhukar et al., 1984; Poland et al., 1985; Safe et al., 1985; Vickers et al., 1985). Structure-activity studies also link the enhanced *in vitro* cell differentiation caused by these compounds to the presence of the Ah receptor (Greenlee et al., 1985b).

However, it has also been noted that the cytosolic receptor binding alone may not be the sole determinant of the capacity for AHH induction (Neal, 1985; Okey and Vella, 1984). In interspecies comparisons there are poor correlations between the concentration of cellular Ah receptor, its ability to

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bind 2,3,7,8-TCDD and AHH induction (Denison and Wilkinson, 1985; Gasiewicz and Rucci, 1984; Neal, 1985); and in the mouse the development of TCDD-induced liver toxicity cannot be ascribed solely to the presence of the Ah receptor (Greig et al., 1984).

A recent review concludes that although there are inconsistencies across species in the Ah receptor being the sole mechanism of toxicity of CDDs and CDFs, the data suggest that the binding of these compounds to the receptor is in some way related to some of the biological effects seen in experimental animals (Neal, 1985).

Table 2 summarizes information on a variety of end points elicited by CDDs and CDFs: acute toxicity, carcinogenicity, reproductive effects, receptor, binding, enzyme induction, and *in vitro* cell transformation. For ease of comparison, the data are normalized to unity for 2,3,7,8-TCDD. For example, 2378-HxCDDs have about 5% the Ah receptor binding strength of 2,3,7,8-TCDD. Their reproductive toxicity and carcinogenic potency are, respectively, about 1% and 4% that of 2,3,7,8-TCDD. Kociba and Cabey (1985) recently presented similar data.

The structure/activity generalizations based on the data in Table 2 support the generalizations in the literature concerning the congeners that are most likely to be of toxic concern (Poland and Knutson, 1982; Gasiewicz and Rucci, 1984; Bandiera et al., 1984). That is, congeners that are substituted in the lateral 2,3,7, and 8 positions are likely to exhibit toxic effects at lower doses than other congeners. This includes the 15 tetra-, penta-, hexa- and heptachlorinated CDDs and CDFs listed in Table 3.[3]

The "2378-TCDD equivalence factors" (TEFs) listed in Tables 1 and 3 were assigned using several criteria.

1. Definitive data on human carcinogenicity.
2. In the absence of definitive data on human carcinogenicity, information on carcinogenic potency is based on long-term animal studies which takes precedence over any other data.
3. When carcinogenic activity has not been demonstrated, data on reproductive effects become determinative because of the significance of this end point in humans. In addition, the estimated exposure levels potentially resulting in reproductive and carcinogenic effects are similar.

[3]The Technical Panel is aware that some investigators (e.g., Grant, 1977; Olie et al., 1983; Commoner et al., 1984; and Ontario government, 1982, 1984) have broadly defined congeners of concern to include those tri- to hepta- congeners which are substituted with at least three chlorines in the four lateral (2, 3, 7, and 8) positions. The toxicity data (Table 2) do not strongly support this extended range of concern. Further, the increased level of complexity invoked by including these additional congeners suggests a greater level of accuracy and resolution than the Technical Panel believes is presently warranted by the TEF approach.

The Technical Panel is also aware that receptor binding data suggest a relatively high potential toxicity for 1,2,4,6,7-PeCDF. Examination of stereochemical models shows that the 4 and 6 positions of CDFs exhibit partial overlap with the lateral chlorine groups of 2,3,7,8-TCDD (Bandiera et al., 1984). However, this increased receptor binding activity is not reflected in an increased potency of 1,2,4,6,7-PeCDF as an enzyme inducer (see Table 2), an end point which has been shown to correlate with subchronic toxicity (Safe et al., 1985). Therefore, the Technical Panel is treating 1,2,4,6,7-PeCDF as a "non-2378-congener" at this time; however, additional data could lead to a change in this position.

1,2,3,6,7- and 2,3,4,6,7-PeCDF are almost as potent as 2378-PeCDF in the induction of AHH activity in human lymphoblastoid cells *in vitro* (see Table 2). However, because this assay seems to yield relative potencies that do not agree with other short-term tests, and because dose-response data are not available for this assay, these data are not included in the overall evaluation at the present time.

Table 2. Potencies of Dioxins Relative to 2,3,7,8-TCDD

Chemical	Guinea pig LD_{50}	Carcino-genicity	Reproductive/ teratogenic effects	Receptor binding	Enzyme Induction: AHH: Animal cells	Enzyme Induction: AHH: Human cells	Enzyme Induction: EROD	Cell keratin.	Flat (XB) cell assay	Immuno-toxicity in vitro
CDDs:										
Mono thru tri	$< 10^{-4}$[e]	–	–	0.001-0.01[e]	< 0.001[f]	–	–	0.01[e]	–	0.005[p]
2378-TCDD	1[a]	1[b]	1[c,i]	1[e]	1[e]	1[m]	1[g]	1[e]	1[l]	1[o,p]
TCDDs	< 0.001[a]	–	< 0.001[k]	< 0.01-0.16[e]	< 0.001-0.02[g]	–	–	< 0.001-0.01[e]	–	–
2378-PeCDD	0.67[a]	–	–	1[e]	0.02-0.2[g]	–	–	0.5[e]	–	–
PeCDDs	0.002[a]	–	–	–	< 0.001[g]	–	–	–	–	–
2378-HxCDDs	0.03[a]	0.04[b]	0.01[c]	0.05[e]	0.001-0.1[g]	–	–	0.005[e]	–	–
HxCDDs	–	–	–	–	< 0.001[g]	–	–	–	–	–
2378-HpCDDs	0.004[a]	–	–	–	0.002-0.004[g,l]	–	–	–	–	–
HpCDDs	0.002[a]	–	–	–	< 0.001[f]	–	–	–	–	–
OCDD	–	–	< 0.00001[k]	–	< 0.001[f]	–	–	–	–	–
CDFs:										
Mono thru tri	–	–	–	≤ 0.001-0.02[d,h]	< 0.001[d]	< 0.001[d]	–	0.001[e]	–	–
2378-TCDF	0.28; 0.5[a]	–	0.03-0.13[i,k]	0.3[e]; 0.24[h]; 0.4[l]	0.01-0.4[f,h,m]	0.4[m]	0.1[h]	0.05[e]	0.1[l]	0.1[o]; 1[p]

Table 2. (continued)

Chemical	Guinea pig LD_{50}	Carcinogenicity	Reproductive/ teratogenic effects	Receptor binding	Enzyme Induction: AHH: Animal Cells	Enzyme Induction: AHH: Human cells	Enzyme Induction: EROD	Cell keratin.	Flat (XB) cell assay	Immunotoxicity in vitro
TCDFs	–	–	–	0.001-0.05[d,e]	≤0.001[d]; 0.04[m]	0.4[m]	≤0.005[d]	–	–	–
2378-PeCDF	–	–	–	0.13[d];0.7[e];0.6[h]	<0.3[d]; 0.4[m]	0.8[m]	0.1[d]	–	–	–
12467-PeCDF	–	–	–	0.15[h]	0.002[h]	–	<0.001[h]	–	–	–
PeCDFs	–	–	–	0.001-0.1[d,e]	<0.001-2[d,n,m]	0.6[m]	≤0.001[h]	–	–	–
2378-HxCDFs	0.017[a]	–	–	0.04-0.5[e,h]	0.05-0.2[h,m]	0.9[m]	0.1-0.5[h]	–	–	–
HxCDFs	–	–	–	0.001[e,h]	0.001[m]; 0.002[h]	–	0.006[h]	–	–	–
2378-HpCDFs	–	–	–	–	0.004[g]	–	–	–	–	–
HpCDFs	–	–	–	<0.001[h]	<0.001[f]	–	–	–	–	–

[a]McKinney and McConnell, 1982; Moore et al., 1979.
[b]U.S. EPA, 1984a.
[c]Murray et al., 1979; Schwetz et al., 1973; Weber et al., 1984.
[d]Bandiera et al., 1983.
[e]Knutson and Poland, 1980.
[f]Bradlaw et al., 1979.
[g]Bradlaw et al., 1980.
[h]Bandiera et al., 1984.
[i]Hassoun et al., 1984.
[j]Gierthy and Crane, 1985.
[k]Weber et al., 1984.
[l]Poland et al., 1979.
[m]Nagayama et al., 1985a,b.
[n]Poland et al., 1976.
[o]Dencker et al., 1985.
[p]Greenlee et al., 1985b.

Table 3. CDD/CDF Isomers of Most Toxic Concern[a]

Dioxin		Dibenzofuran	
Isomer	TEF[b]	Isomer	TEF[b]
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.01
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.01
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.01
		2,3,4,6,7,8-HxCDF	0.01
1,2,3,4,6,7,8-HpCDD	0.001	1,2,3,4,6,7,8-HpCDF	0.001
		1,2,3,4,7,8,9-HpCDF	0.001

[a] *In each homologous group, the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.*
[b] *TEF = Toxicity Equivalence Factor = relative toxicity assigned.*

4. When neither carcinogenic nor reproductive effects have been demonstrated, the weight of the evidence of the *in vitro* test data is estimated. To simplify the approach and to acknowledge the approximate nature of the approach, these estimates are rounded off to the nearest order of magnitude. Somewhat more weight is placed on data from receptor binding interaction and oxidative enzyme induction, due to the correlations between these *in vitro* end points and certain *in vivo* systemic efforts; e.g., thymic atrophy and body weight loss.

The above criteria were applied as described below.

1. Since the primary concern is with chronic effects, the relative carcinogenicity responses (Table 2) for 2,3,7,8-TCDD and the mixture of two 2378-HxCDDs[4] were used to generate the TEF for 2378-PeCDD. The TEF for 2378-PeCDD (0.5) is the arithmetic mean of the carcinogenic potency values for 2,3,7,8-TCDD (1) and 2378-HxCDDs (0.04). Data on receptor binding, enzyme induction, and cell keratinization generally support this value.
2. 2,3,7,8-TCDF is assigned a TEF of 0.1 primarily because it is 1 to 2 orders of magnitude (OMs) less potent than 2,3,7,8-TCDD in reproductive toxicity tests. Also, it is about one OM less potent than 2,3,7,8-TCDD in the *in vitro* tests.
3. The 2378-PeCDF congeners are assigned a TEF of 0.1 due to the responses seen in *in vitro* tests. Greater reliance was placed on the animal enzyme induction studies due to the more significant correlations observed between this end point and subchronic responses than have been observed with the receptor binding end point. The human cell data were accorded less weight because these experiments were conducted at only one exposure concentration.
4. Because *in vitro* data in general show HxCDFs to be about one tenth as potent as PeCDFs, their TEF is assigned a value of 0.01 (0.1/10). Further, the data generally suggest that CDFs are somewhat less toxic than the analogous CDDs. Therefore, the TEF for 2378-HxCDFs should be less than that of the 2378-HxCDDs (0.04).

[4] See Appendix A, item 8, for explanation of notation.

5. The 2378-HpCDDs and 2378-HpCDFs are assigned TEFs 3 OM less than that for 2,3,7,8-TCDD because the enzyme induction potencies of these congeners differ from that of 2,3,7,8-TCDD by about this factor.
6. Based on the data in Table 2, the non-2378-substituted isomers are 1 to 2 OMs less potent than the 2378-substituted isomers. Since these data are limited to *in vitro* systems, a factor of 0.01 is applied to the non-2378-substituted, as compared to the 2378-substituted congeners.

With the exception of 2,3,7,8-TCDD, the 2378-HxCDDs, and 2378-TCDF, the TEFs are not based on the results of major animal (reproductive, carcinogenic) studies. Generally, TEFs are based on estimates of the relative toxicity in *in vitro* tests whose relationship to the chronic effects of concern is largely presumptive. However, as discussed above, studies on systemic effects continue to reinforce the view that the short-term assays provide important fundamental information on the toxicity of the CDDs and CDFs.

In summary, the Forum concludes that there is a sufficiently plausible basis for the TEF approach of estimating risks associated with exposures to CDDs and CDFs and recommends that the Agency adopt the approach, on an interim basis, as a matter of science policy. The TEFs should be revised as additional scientific information is developed. It should be noted that this general approach to estimating such CDD/CDF risks has been taken by other regulatory groups (see Table 1 and Appendix B).

V. Applications to Risk Assessment

In general, as assessment of the human health risk of a mixture of CDDs and CDFs, using the TEF approach, involves the following steps:

1. Analytical determination of the CDDs and CDFs in the sample.
2. Multiplication of congener concentrations in the sample by the TEFs in Table 1 to express the concentration in terms of 2378-TCDD equivalents.
3. Summation of the products in step 2 to obtain the total 2378-TCDD equivalents in the sample.
4. Determination of human exposure to the mixture in question, expressed in terms of 2378-TCDD equivalents.
5. Combination of exposure from step 4 with toxicity information on 2,3,7,8-TCDD (usually carcinogenicity and/or reproductive effects) to estimate risks associated with the mixture.

In cases in which the concentrations of the 15 congeners are known:

$$\text{2378-TCDD Equivalents} = \Sigma\,(\text{TEF of each 2378-CDD/CDF congener} \times \text{the concentration of the respective congener}) + \Sigma\,(\text{TEF of each non-2378-CDD/CDF congener} \times \text{the concentration of the respective congener})$$

Samples of this calculation for several environmental mixtures are provided in Table 4.

In cases where only the concentration of homologous groups is known, i.e., no isomer-specific data are available, different approaches are possible. For example, the assumption that the 2378-congeners of concern constitute all of the CDDs and CDFs present in the mixture is likely to provide an upper-bound, most conservative estimate of the toxicity. Alternatively, one could assume that the occurrence of each of the congeners in the mixture has equal probability (Olie et al., 1983; Commoner et al., 1984). For instance 2,3,7,8-TCDD is one of 22 possible TCDDs and would constitute about 4% of a mixture of isomers occurring with equal probability. In other situations particular knowledge of chemical reaction parameters, process conditions, and results from related studies (e.g., congener distributions in emissions form combustion sources) might enable one to estimate the relative occurrence of 2378-congeners. However, one must be careful to explicitly explain and justify whatever assumptions are made. Table 5 illustrates the results obtained using different methods to estimate the proportion of 2378 to non-2378 isomers in the absence of analytical data for individual isomers.

The calculated 2378-TCDD equivalents can then be used to assess the health risk of a mixture. As an explicit example, consider a municipal solid waste (MSW) combustor whose particulate emissions, the CDD/CDF mixture in question, are the same as the electrostatic precipitator (ESP) catch cited in columns 5 and 6 of Table 4. The sample is estimated to contain 32 ppb 2378-TCDD equivalents; i.e., 32 picograms of 2378-TCDD equivalents per milligram of mixture. Suppose that an exposure analysis indicates that a person living downwind from the incinerator receives an average daily dose of 1 ng of the mixture/kg body weight resulting from inhalation (i.e., without

consideration of other possible routes of exposure). This exposure estimate is combined with the upper-bound carcinogenic potency of 2,3,7,8-TCDD (1.6×10^5 per mg/kg-day [U.S. EPA, 1984b]) to generate the upper 95% limit of the excess risk of developing cancer (from inhalation exposure alone) for a person living downwind from the facility emitting the mixture under consideration, assuming lifetime exposure:

upper 95% limit of excess cancer risk resulting from inhalation exposure
= [potency] × [exposure]
= [1.6×10^5 per mg 2,3,7,8-TCDD/kg-day]
× [32 pg TCDD/mg mixture × 10^{-9} mg 2,3,7,8-TCDD/pg
× 1 ng mixture/kg-day × 10^{-6} mg mixture/ng mixture].

Table 4. PCDDs/PCDFs in Some Environmental Samples

		Air partics. St. Louis[e]		MSW ESP dust[e]		Lake sediment[e]		1982 Milorganite[d]		MSW fly ash[f] Ontario		MSW fly ash[f] Oslo	
Isomer	TEF	CDD/F conc. (ppb)	TCDD eqts. (ppb)	CDD/F conc. (ppb)	TCDD eqts. (ppb)	CDD/F conc. (ppb)	TCDD eqts. (ppb)	CDD/F conc. (ppt)	TCDD eqts. (ppt)	CDD/F conc. (ppt)	TCDD eqts. (ppt)	CDD/F conc. (ppt)	TCDD eqts. (ppt)
TCDDs	1	0.2	0.2	5	5	0	0	206	206	541	541	ND	–
PeCDDs	0.5	1	0.5	10	5	0.1	0.05	–	–	467	234	11	5.5
HxCDDs	0.04	1.2	0.048	160	6.4	0.34	0.014	2768	110.7	591	24	51	2
HpCDDs	0.001	25	0.025	120	0.12	0.5	0.001	7600	7.6	434	0.43	119	0.12
OCDD	0	170	0	260	0	1.3	0	60000	0	467	0	186	0
TCDFs	0.1	–	–	40	4	0.13	0.013	–	–	–	–	–	–
PeCDFs	0.1	–	–	80	8	0.14	0.014	–	–	–	–	–	–
HxCDFs	0.01	–	–	280	2.8	0.38	0.004	–	–	–	–	–	–
HpCDFs	0.001	–	–	160	0.16	1.13	0.001	–	–	–	–	–	–
OCDF	0	–	–	40	0	0.14	0	–	–	–	–	–	–
Total TCDD eqts.			0.08		32		0.10		324		799		7.3

Table 4. (continued)

		Thermal degradation prods. from dielectric fluids[a]				Japanese MSW[b]				Commercial CPs				Soot from PCB fire[g]	
		Run 8-13-40		Run 8-30-61 ASKL		Pt. A TEF		Pt. B TEF		246TCP[c]		PCP[c]			
Isomer	TEF	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.
		(ng)		(μg)		[lb/MMBTU(x10^{-6})]				(ppm)		(ppm)		(ppm)	
TCDDs															
2378	1	0	0	0	0	0.1	0.1	0.58	0.58	<0.1	–	<0.1	–	0.6	0.6
other	0.01													0.6	0.01
PeCDDs															
2378	0.5	0	0	0	0	0.07	0.035	0.47	0.24	<0.1	–	<0.1	–	2.5	1.25
other	0.002													2.5	0.01
HxCDDs															
2378	0.04	0	0	0	0	0.04	0.002	0.36	0.014	<1	–	2.5	0.1	1.1	0.04
other	0.0004													3.6	–
HpCDDs															
2378	0.001	0	0	330	0.33	0.02	<0.001	0.08	<0.001	<1	–	175	0.18	3	–
other	0.00001													4	–
OCDD	0	0	0	37	0	0.01	0	0.04	0	<1	0	500	0	2	0

Table 4. (continued)

		Thermal degradation prods. from dielectric fluids[a]				Japanese MSW[b]				Commercial CPs				Soot from PCB fire[g]	
		Run 8-13-40		Run 8-30-61 ASKL		Pt. A TEF		Pt. B TEF		246TCP[c]		PCP[c]			
Isomer	TEF	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.
		(ng)		(μg)		[lb/MMBTU(x10^{-6})]				(ppm)		(ppm)		(ppm)	
TCDDs															
2378	0.1	690	69	1400	140	1.31	0.131	1.25	0.125	1.5	0.15	<0.1	–	12	1.2
other	0.001													16	0.01
PeCDDs															
2378	0.1	43	4.3	6400	640	0.38	0.038	0.46	0.046	17.5	1.75	<0.1	–	358	35.8
other	0.001													312	0.3
HxCDDs															
2378	0.01	7	0.07	910	9.1	0.06	0.006	0.06	0.006	36	3.6	<0.3	–	670	6.7
other	0.0001													295	0.03
HpCDDs															
2378	0.001	0	0	29	0.029	0.01	<0.001	0.02	<0.001	4.8	0.005	19	0.019	285	0.29
other	0.00001													172	0
OCDD	0	0	0	3.4	0	0.004	0	0.01	0	<1	0	25	0	40	0
Total TCDD eqts.			73		789		0.3		1.02		5.5		0.3		46

[a]U.S. EPA, 1984c.
[b]Cooper Engineers, 1984.
[c]Rappe, 1984.
[d]Lamparski et al., 1984.
[e]Czuwa and Hites, 1984.
[f]Tong et al., 1984.
[g]Des Rosiers, 1984.

Table 5. · Use of the TEF Approach

Isomer	TEF	Propn. factor	PCB fire soot[a] CDD/F conc. (ppm)	PCB fire soot[a] TCDD eqts. (ppm) A[c]	B[c]	C[c]	D[c]	MSW fly ash[b] Sample 1 CDD/F conc. (ppb)	Sample 1 TCDD eqts. (ppb) A[c]	B[c]	D[c]	Sample 2 CDD/F conc. (ppb)	Sample 2 TCDD eqts. (ppb) A[c]	B[c]	D[c]
Total TCDDs	1	1	1.2	1.2				85	85			2.7	2.7		
2378-TCDDs	1	0.05	1.2		0.2	0.6		85		4.3		2.7		0.1	
other TCDDs	0.01	0.95	1.2		—[d]	—		85		0.8		2.7		—	
Total PeCDDs	0.5	1	5.0	2.5				213	107			6.6	3.3		
2378-PeCDDs	0.5	0.07	5.0		0.2	1.3		213		7.0		6.6		0.2	
other PeCDDs	0.005	0.93	5.0		—	—		213		1.0		6.6		—	
Total HxCDDs	0.04	1	4.7	0.2				354	14.2			11.6	0.5		
2378-HxCDDs	0.04	0.3	4.7		0.1	—		354		4.3		11.6		0.1	
other HxCDDs	0.0004	0.7	4.7		—	—		354		0.1		11.6		—	
Total HpCDDs	0.001	1	7	—		—		184	0.2			5.7	—		
2378-HpCDDs	0.001	0.5	7		—			184		0.1		5.7		—	
other HpCDDs	0.00001	0.5	7		—			184		—		5.7		—	
Total TCDFs	0.1	1	28	2.8				209	20.9			7.0	0.7		
2378-TCDFs	0.1	0.03	28		0.1	1.2		209		0.6		7.0		—	
other TCDFs	0.001	0.97	28		—	—		209		0.2		7.0		—	

Table 5. (continued)

Isomer	TEF	Propn. factor	PCB fire soot[a] CDD/F conc. (ppm)	PCB fire soot[a] TCDD eqts. (ppm) A[c]	B[c]	C[c]	D[c]	MSW fly ash[b] Sample 1 CDD/F conc. (ppb)	Sample 1 TCDD eqts. (ppb) A[c]	B[c]	D[c]	Sample 2 CDD/F conc. (ppb)	Sample 2 TCDD eqts. (ppb) A[c]	B[c]	D[c]
Total PeCDFs	0.1	1	670	67				549	54.9			17.8	1.8		
2378-PeCDFs	0.1	0.07	670		4.7	35.8		549		3.8		17.8		0.1	
other PeCDFs	0.001	0.93	670		0.6	0.3		549		0.5		17.8		—	
Total HxCDFs	0.01	1	965	9.7				1082	10.8			32.1	0.3		
2378-HxCDFs	0.01	0.25	965		2.4	6.7		1082		2.7		32.1		0.1	
other HxCDFs	0.0001	0.75	965		0.1	—		1082		0.1		32.1		—	
Total HpCDFs	0.001	1	460	0.5				499	0.5			10.9		—	
2378-HpCDFs	0.001	0.50	460		0.2	0.3		499		0.2		10.9		—	
other HpCDFs	0.00001	0.50	460		—	—		499		—		10.9		—	
Total estimated TCDD equivalents (TEF)				84	8	46			294	26			3	1	
Measured TCDD Equivalents															
AHH bioassay							—				4				
EROD bioassay							—				5				
Receptor binding assay							—				32				
Acute toxicity bioassay							58				—				

Table 5. (continued)

Isomer	TEF	Propn. factor	MSW fly ash[b] Sample 3 CDD/F conc. (ppb)	Sample 3 TCDD eqts. (ppb) A[c]	Sample 3 TCDD eqts. (ppb) B[c]	Sample 3 TCDD eqts. (ppb) D[c]	Sample 4 CDD/F conc. (ppb)	Sample 4 TCDD eqts. (ppb) A[c]	Sample 4 TCDD eqts. (ppb) B[c]	Sample 4 TCDD eqts. (ppb) D[c]
Total TCDDs	1	1	12.9	12.9			2.4	2.4		
2378-TCDDs	1	0.05	12.9		0.6		2.4		0.1	
other TCDDs	0.01	0.95	12.9		0.1		2.4		–	
Total PeCDDs	0.5	1	37.5	18.8			7.9	4.0		
2378-PeCDDs	0.5	0.07	37.5		1.3		7.9		0.3	
other PeCDDs	0.005	0.93	37.5		0.2		7.9		–	
Total HxCDDs	0.04	1	75	3			9.7	0.4		
2378-HxCDDs	0.04	0.3	75		0.9		9.7		0.1	
other HxCDDs	0.0004	0.7	75		–		9.7		–	
Total HpCDDs	0.001	1	41.9	–			9.1	–		
2378-HpCDDs	0.001	0.5	41.9		–		9.1		–	
other HpCDDs	0.00001	0.5	41.9		–		9.1		–	
Total TCDFs	0.1	1	8.2	0.8			4.4	0.4		
2378-TCDFs	0.1	0.03	8.2		–		4.4		–	
other TCDFs	0.001	0.97	8.2		–		4.4		–	
Total PeCDFs	0.1	1	19.8	2.0			21.0	2.1		
2378-PeCDFs	0.1	0.07	19.8		0.1		21.0		0.1	
other PeCDFs	0.001	0.93	19.8		–		21.0		–	

Table 5. (continued)

Isomer	TEF	Propn. factor	MSW fly ash[b] Sample 3 CDD/F conc. (ppb)	Sample 3 TCDD eqts. (ppb) A[c]	Sample 3 TCDD eqts. (ppb) B[c]	Sample 3 TCDD eqts. (ppb) D[c]	Sample 4 CDD/F conc. (ppb)	Sample 4 TCDD eqts. (ppb) A[c]	Sample 4 TCDD eqts. (ppb) B[c]	Sample 4 TCDD eqts. (ppb) D[c]
Total HxCDFs	0.01	1	38.7	0.4			21.6	0.2		
2378-HxCDFs	0.01	0.25	38.7		0.1		21.6		0.1	
other HxCDFs	0.0001	0.75	38.7		—		21.6		—	
Total HpCDFs	0.001	1	20.6	—			16.6	—		
2378-HpCDFs	0.001	0.50	20.6		—		16.6		—	
other HpCDFs	0.00001	0.50	20.6		—		16.6		—	
Total estimated TCDD equivalents (TEF)				38	2			9	0.7	
Measured TCDD Equivalents										
AHH bioassay						4				2
EROD bioassay						5				2
Receptor binding assay						65				11
Acute toxicity bioassay						—				—

[a]Des Rosiers, 1984, assuming only homologue-specific concentrations are known (for isomer-specific analyses; see Table 4).
[b]Sawyer et al., 1983.
[c]A = estimated assuming 2378-isomers constitute 100% of a homologous group.
B = estimated assuming occurrence of all isomers in a homologous group is equally probable (thus using the proportionality factor in column three).
C = estimated by utilizing isomer-specific analyses (see Table 4).
D = estimated by direct bioassay.
[d]Values rounding off to less than 0.1 are omitted.

VI. Comparison of the TEF Approach with Results of Biological Testing

A limited number of *in vivo* and *in vitro* approaches have been employed in assessing the toxicity of complex mixtures of CDDs and CDFs. While the results from these attempts are not definitive, it is instructive to compare those results with the results from the TEF approach proposed here.

Eadon et al. (1982) investigated the toxicity of CDD/CDF-contaminated soot associated with a fire involving PCB-containing electrical equipment. Using the results from acute *in vivo* toxicity (LD_{50}) studies in which the soot was the test substance, the researchers determined that it had the acute toxicity expected of material containing about 60 times the amount of 2,3,7,8-TCDD actually found by GC/MS analysis.

Table 5 illustrates the results of employing the TEF approach through three different procedures, each of which depends upon the results of GC/MS analysis of the soot. In the first instance (A, in Table 5), the analytical data have been consolidated to totals within a homologous class. These concentrations are treated as if they consisted completely of 2378-members of the class and, therefore, are multiplied by the TEF appropriate for the 2378-members of the class. The resulting estimate of 2378-TCDD equivalents by this procedure is about 80.

In procedure B the assumption is made that the occurrence of each of the congeners in a homologous class is equally probable; e.g., the concentration of 2,3,7,8-TCDD is 1/22 (about 5%) of the concentration of the total TCDDs. This approach leads to an estimate of the total 2378-TCDD equivalents of 8.

A rather unique data base exists in the case of the soot from this fire in that an extensive isomer-specific analysis of the sample is available (as cited in Des Rosiers, 1984). Therefore, the full array of TEFs from Table 1 (using the current EPA recommendations) can be applied. This procedure (C in Table 5) results in an estimate of roughly 50 for the total 2378-TCDD equivalents in the sample.

As might be expected, the most conservative of these procedures, A, leads to the highest estimate. Approach B (using theoretical probability of occurrence) leads to an estimate that is about 10-fold lower than the isomer-specific results C, reflecting the fact that the 2378-congeners are present in somewhat higher than "equal probability" proportions in this particular soot sample. Given the complexity of the analysis involved, the approximate nature of the TEF method, and the vagaries of the assay, a major feature of note in Table 5 regarding the soot samples is that the results of procedures A, B, and C span a range of only one order of magnitude and bracket the bioassay estimate, reported by Eadon et al. (1982).

Table 5 also shows the results of the application of approaches A and B to published results of homologue-specific CDD and CDF concentrations in fly ash from four municipal solid waste combustors (Sawyer et al., 1983). In addition, extracts from the fly ash samples were analyzed by three bioassay techniques (AHH induction, EROD induction, and receptor binding). Again, the calculated results span an order of magnitude, with the bioassay results lying within or close to this range.

These data suggest that the TEF approach is likely to be a useful interim tool for the rough (order of magnitude) estimation of the toxicity of complex

mixtures of CDDs and CDFs. The availability of additional data comparing the results of analytical and biological assays will enable a conclusion regarding the preferred method of estimating TEFs (e.g., method A or B of Table 5).

VII. Research Needs

The Forum recommends that the Agency support research that would allow actual measurement of mixtures containing CDDs and CDFs, rather than drawing inferences from component toxicity. The results of this research could reduce the need for the TEF approach. In addition, research should be conducted in order to provide a firmer basis for, and to guide appropriate modification of, the TEF approach. Several areas of research are appropriate for these purposes.

1. Validation and completion of the *in vitro* test data such as those listed in Table 2.
2. Investigation of the relationships between short-term *in vivo* and *in vitro* tests and the toxic end points of concern; i.e., carcinogenicity, reproductive toxicity, immunotoxicity, and other significant human health effects resulting from CDD/CDF exposure.
3. Determination of the impact of pharmacodynamics, including bioavailability, potential for absorption, and toxic potencies of metabolites of CDDs and CDFs in *in vitro* tests, relative to the potencies of the parent compounds. As pointed out by several reviewers, this would enable refinement of the TEF approach.
4. Investigation of additional short-term assays which can test the mechanistic hypotheses underlying the TEF approach.

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Appendix A
Nomenclature

The following terminology and abbreviations are used in this document:

1. The term "congener" refers to any one particular member of the same chemical family; e.g., there are 75 congeners of chlorinated dibenzo-*p*-dioxins.
2. The term "homologue" refers to a group of structurally related chemicals that have the same degree of chlorination. For example, there are eight homologues of CDDs, monochlorinated through octochlorinated.
3. The term "isomer" refers to substances that belong to the same homologous class. For example, there are 22 isomers that constitute the homologues of TCDDs.
4. A specific congener is denoted by unique chemical notation. For example, 2,4,8,9-tetrachlorodibenzofuran is referred to as 2,4,8,9-TCDF.
5. Notation for homologous classes is as follows:

Dibenzo-*p*-dioxin	D
Dibenzofuran	F

No. of halogens	Acronym	Example
1	M	
2	D	2,4-DCDD
3	Tr	
4	T	1,4,7,8-TCDD
5	Pe	
6	Hx	
7	Hp	
8	O	
1 through 8	CDDs and CDFs	

6. Dibenzo-*p*-dioxins and dibenzofurans that are chlorinated at the 2,3,7, and 8 positions are denoted as "2378" congeners, except when 2,3,7,8-TCDD is uniquely referred to; e.g., 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF are both referred to as "2378-PeCDFs."

Appendix B
Comparison of Different Approaches to Calculating 2378-TCDD Equivalents

Table 1 in the text lists a number of different approaches for calculating 2378-TCDD toxicity equivalents. Five of the approaches (those that deal with 4-position 2378-substituted congeners, but not 3-position substituted congeners) were applied to the data in Table 4 in the text.

These approaches were also applied to some of the data included in Table I of the Report of the Citizens Advisory Committee on Resource Recovery in Brooklyn (March, 1985), produced by Ketcham and the Mt. Sinai School of Medicine.

A summary comparison of the relative results is found in Table B-1, with the supporting tables (Tables B-2 through B-13) attached. (Note that the units of mass emission are not the same for all of the facilities. Therefore, comparison of absolute numbers between facilities may be invalid).

These data indicate that, in general, the methods used by the Swiss government, New York State, and the U.S. EPA (the 1981 approach and the 1985 proposal) all generate results which are within an order of magnitude of each other. This suggests that, within the range considered, the results are not particularly sensitive functions of the TEFs selected.

The procedure recommended by the state of California, however, gives results which are roughly an order of magnitude higher than those generated by the other approaches. In general, the greater the contribution from the TCDDs, the greater the similarity in the results of the methods. This is due to the fact that all methods assign a TEF of 1 for 2,3,7,8-TCDD (and 1 to all TCDDs, when isomer-specific analyses are not available). Because higher chlorinated CDDs and CDFs contribute significantly to the total, the disparity is greater between the state of California results and those produced by the other methods, since California assumes that all 2378-substituted CDDs and CDFs are as potent as 2,3,7,8-TCDD. The other methods acknowledge, to one degree or another, the reduced toxicity of higher chlorinated species; see Table 2.

Table B-1. Relative 2378-TCDD Equivalents[a]

Source	EPA'85	EPA '81	Swiss	NY	CA
St. Louis air particulates	1	0.3	1	2	40
PCB fire soot (isomer-specific)	1	0.03	4	3	30
MSW ESP dust	1	0.2	3	2	30
Lake sediment	1	—	2	2	30
Milorganite	1	0.6	2	0.9	30
Oslo MSW fly ash	1	—	1	2	20
Ontario MSW fly ash	1	0.8	1	2	3
Japanese plant A	1	0.3	1	2	7
Japanese plant B	1	0.6	0.8	2	3
Albany	1	0.3	0.4	2	5
Wright-Patterson (best)	1	0.2	2	3	20
Wright-Patterson (worst)	1	0.4	2	2	20

[a]Calculated using the Toxicity Equivalence Factors shown in Table 1.

Table B-2. Calculation of 2378-TCDD Toxicity Equivalents for St. Louis Air Particulates Using Homologue-Specific Data

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.2	1	0.2	1	0.2	1	0.2	1	0.2	1	0.2
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	1	0.5	0.5	0	0	0.1	0.1	1	1	1	1
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	1.2	0.04	0.048	0	0	0.1	0.12	0.03	0.036	1	1.2
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	25	0.001	0.025	0	0	0.01	0.25	0	0	1	25
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	170	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-2. (continued)

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.7		0.2		0.7		1.2		27.4

Table B-3. Calculation of 2378-TCDD Toxicity Equivalents for PCB Fire Soot Using Isomer-Specific Data

Compound	CDD/F conc. (ppm)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.6	1	0.6	1	0.6	1	0.6	1	0.6	1	0.6
TCDDs	0.6	0.01	0.006	1	0.6	0.01	0.006	0	0	0	0
2378-PeCDD	2.5	0.5	1.25	0	0	0.1	0.25	1	2.5	1	2.5
PeCDDs	2.5	0.005	0.0125	0	0	0.1	0.25	0	0	0	0

Table B-3. (continued)

Compound	CDD/F conc. (ppm)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)
2378-HxCDD	1.1	0.04	0.044	0	0	0.1	0.11	0.03	0.033	1	1.1
HxCDDs	3.6	0.0004	0.00144	0	0	0.1	0.36	0	0	0	0
2378-HpCDD	3	0.001	0.003	0	0	0.01	0.03	0	0	1	3
HpCDDs	4	0.00001	0.00004	0	0	0.01	0.04	0	0	0	0
OCDD	2	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	12	0.1	1.2	0	0	0.1	1.2	0.33	3.96	1	12
TCDFs	16	0.001	0.016	0	0	0.1	1.6	0	0	0	0
2378-PeCDF	358	0.1	35.8	0	0	0.1	35.8	0.33	118.14	1	358
PeCDFs	312	0.001	0.312	0	0	0.1	31.2	0	0	0	0
2378-HxCDF	670	0.01	6.7	0	0	0.1	67	0.01	6.7	1	670
HxCDFs	295	0.0001	0.0295	0	0	0.1	29.5	0	0	0	0
2378-HpCDF	285	0.001	0.285	0	0	0.1	28.5	0	0	1	285
HpCDFs	172	0.00001	0.00172	0	0	0	0	0	0	0	0
OCDF	40	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			46		1.2		196		132		1332

Table B-4. Calculation of 2378-TCDD Toxicity Equivalents for MSW ESP Dust Using Homologue-Specific Data and 2378 TEFs

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	5	1	5	1	5	1	5	1	5	1	5
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	10	0.5	5	0	0	0.1	1	1	10	1	10
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	160	0.04	6.4	0	0	0.1	16	0.03	4.8	1	160
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	120	0.001	0.12	0	0	0.01	1.2	0	0	1	120
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	260	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	40	0.1	4	0	0	0.1	4	0.33	13.2	1	40
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	80	0.1	8	0	0	0.1	8	0.33	26.4	1	80
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	280	0.01	2.8	0	0	0.1	28	0.01	2.8	1	280
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-4. (continued)

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
2378-HpCDF	160	0.001	0.16	0	0	0.1	16	0	0	1	160
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	40	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			31		5		79		62		855

Table B-5. Calculation of 2378-TCDD Toxicity Equivalents for Lake Sediment Using Homologue-Specific Data

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0	1	0	1	0	1	0	1	0	1	0
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.1	0.5	0.05	0	0	0.1	0.01	1	0.1	1	0.1
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.34	0.04	0.0136	0	0	0.1	0.034	0.03	0.0102	1	0.34
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0

Table B-5. (continued)

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
2378-HpCDD	0.5	0.001	0.0005	0	0	0.01	0.005	0	0	1	0.5
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	1.3	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	0.13	0.1	0.013	0	0	0.1	0.013	0.33	0.0429	1	0.13
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.14	0.1	0.014	0	0	0.1	0.014	0.33	0.0462	1	0.14
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.38	0.01	0.0038	0	0	0.1	0.038	0.01	0.0038	1	0.38
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	1.13	0.001	0.00113	0	0	0.1	0.113	0	0	1	1.13
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.14	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.1		0		1.2		0.2		2.7

Table B-6. Calculation of 2378-TCDD Toxicity Equivalents for Milorganite Using Homologue-Specific Data

2Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	206	1	206	1	206	1	206	1	206	1	206
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0	0.5	0	0	0	0.1	0	1	0	1	0
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	2768	0.04	110.72	0	0	0.1	276.8	0.03	83.04	1	2768
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	7600	0.001	7.6	0	0	0.01	76	0	0	1	7600
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	60000	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-6. (continued)

Compound	CDD/F conc. (ppt)	EPA 1985 TEFs	EPA 1985 TEs (ppt)	EPA 1981 TEFs	EPA 1981 TEs (ppt)	Switzerland TEFs	Switzerland TEs (ppt)	New York TEFs	New York TEs (ppt)	California TEFs	California TEs (ppt)
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			324		206		559		289		10600

Table B-7. Calculation of 2378-TCDD Toxicity Equivalents for Oslo MSW Fly Ash Using Homologue-Specific Data

Compound	CDD/F conc. (ppt)	EPA 1985 TEFs	EPA 1985 TEs (ppt)	EPA 1981 TEFs	EPA 1981 TEs (ppt)	Switzerland TEFs	Switzerland TEs (ppt)	New York TEFs	New York TEs (ppt)	California TEFs	California TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	NA	1	0	1	0	1	0	1	0	1	0
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	11	0.5	5.5	0	0	0.1	1.1	1	11	1	11
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	51	0.04	2.04	0	0	0.1	5.1	0.03	1.53	1	51
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0

Table B-7. (continued)

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
2378-HpCDD	119	0.001	0.119	0	0	0.01	1.19	0	0	1	119
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	186	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1*	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			7.7		0		7.4		12.5		181

Table B-8. Calculation of 2378-TCDD Toxicity Equivalents for Ontario MSW Fly Ash Using Homologue-Specific Data

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	541	1	541	1	541	1	541	1	541	1	541
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	467	0.5	233.5	0	0	0.1	46.7	1	467	1	467
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	591	0.04	23.64	0	0	0.1	59.1	0.03	17.73	1	591
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	434	0.001	0.434	0	0	0.01	4.34	0	0	1	434
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	467	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-8. (continued)

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			799		541		651		1026		2033

Table B-9. Calculation of 2378-TCDD Toxicity Equivalents for MSW at Japanese Plant A Using Homologue-Specific Data

Compound	CDD/F conc.[a]	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.1	1	0.1	1	0.1	1	0.1	1	0.1	1	0.1
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.07	0.5	0.035	0	0	0.1	0.007	1	0.07	1	0.07
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.04	0.04	0.0016	0	0	0.1	0.004	0.03	0.0012	1	0.04
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0

Table B-9. (continued)

Compound	CDD/F conc.[a]	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]
2378-HpCDD	0.02	0.001	0.00002	0	0	0.01	0.0002	0	0	1	0.02
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	0.01	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	1.31	0.1	0.131	0	0	0.1	0.131	0.33	0.4323	1	1.31
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.38	0.1	0.038	0	0	0.1	0.038	0.33	0.1254	1	0.38
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.06	0.01	0.0006	0	0	0.1	0.006	0.01	0.0006	1	0.06
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	0.01	0.001	0.00001	0	0	0.1	0.001	0	0	1	0.01
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.004	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.3		0.1		0.3		0.7		2.0

[a]Units = lb/MM BTU($\times 10^{-6}$).

Table B-10. Calculation of 2378-TCDD Toxicity Equivalents for MSW at Japanese Plant B Using Homologue-Specific Data

Compound	CDD/F conc.[a]	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.58	1	0.58	1	0.58	1	0.58	1	0.58	1	0.58
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.47	0.5	0.235	0	0	0.1	0.047	1	0.47	1	0.47
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.36	0.04	0.0144	0	0	0.1	0.036	0.03	0.0108	1	0.36
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	0.08	0.001	0.00008	0	0	0.01	0.0008	0	0	1	0.08
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	0.04	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	1.25	0.1	0.125	0	0	0.1	0.125	0.33	0.4125	1	1.25
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.46	0.1	0.046	0	0	0.1	0.046	0.33	0.1518	1	0.46
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.06	0.01	0.0006	0	0	0.1	0.006	0.01	0.0006	1	0.06
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-10. (continued)

Compound	CDD/F conc.[a]	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]	TEFs	TEs[a]
2378-HpCDF	0.02	0.001	0.00002	0	0	0.1	0.002	0	0	1	0.02
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.01	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			1.0		0.6		0.8		1.6		3.3

[a]Units = lb/MM BTU($x10^{-6}$).

Table B-11. Calculation of 2378-TCDD Toxicity Equivalents for MSW at Albany Using Homologue-Specific Data

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.45	1	0.45	1	0.45	1	0.45	1	0.45	1	0.45
TCDDs	14	0.01	0.14	1	14	0.01	0.14	0	0	0	0
2378-PeCDD	97	0.5	48.5	0	0	0.1	9.7	1	97	1	97
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	53	0.04	2.12	0	0	0.1	5.3	0.03	1.59	1	53
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0

Table B-11. (continued)

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
2378-HpCDD	71	0.001	0.071	0	0	0.01	0.71	0	0	1	71
HpCDDs	0	0.00001	0	0	0	0.01	C	0	0	0	0
OCDD	10	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	2.1	0.1	0.21	0	0	0.1	0.21	0.33	0.693	1	2.1
TCDFs	33	0.001	0.033	0	0	0.1	3.3	0	0	0	0
2378-PeCDF	21	0.1	2.1	0	0	0.1	2.1	0.33	6.93	1	21
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	4	0.01	0.04	0	0	0.1	0.4	0.01	0.04	1	4
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	1	0.001	0.001	0	0	0.1	0.1	0	0	1	1
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	2	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			54		14		22		107		250

Table B-12. Calculation of 2378-TCDD Toxicity Equivalents for WP AFB (Best) Using Homologue-Specific Data

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.4	1	0.4	1	0.4	1	0.4	1	0.4	1	0.4
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.4	0.5	0.2	0	0	0.1	0.04	1	0.4	1	0.4
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	1	0.04	0.04	0	0	0.1	0.1	0.03	0.03	1	1
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	3	0.001	0.003	0	0	0.01	0.03	0	0	1	3
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	3	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	8	0.1	0.8	0	0	0.1	0.8	0.33	2.64	1	8
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	3	0.1	0.3	0	0	0.1	0.3	0.33	0.99	1	3
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	4	0.01	0.04	0	0	0.1	0.4	0.01	0.04	1	4
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0

Table B-12. (continued)

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
2378-HpCDF	9	0.001	0.009	0	0	0.1	0.9	0	0	1	9
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	2	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			1.8		0.4		3.0		4.5		28.8

Table B-13. Calculation of 2378-TCDD Toxicity Equivalents for WP AFB (Worst) Using Homologue-Specific Data

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	4	1	4	1	4	1	4	1	4	1	4
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	3	0.5	1.5	0	0	0.1	0.3	1	3	1	3
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	6	0.04	0.24	0	0	0.1	0.6	0.03	0.18	1	6
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0

Table B-13. (continued)

Compound	CDD/F conc. (ng/m^3)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)	TEFs	TEs (ng/m^3)
2378-HpCDD	32	0.001	0.032	0	0	0.01	0.32	0	0	1	32
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	16	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	31	0.1	3.1	0	0	0.1	3.1	0.33	10.23	1	31
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	15	0.1	1.5	0	0	0.1	1.5	0.33	4.95	1	15
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	23	0.01	0.23	0	0	0.1	2.3	0.01	0.23	1	23
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	93	0.001	0.093	0	0	0.1	9.3	0	0	1	93
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	8	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			11.0		4		21.4		22.6		207

Part II

1989 Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-Dioxins and -Dibenzofurans (CDDs and CDFs)

March 1989

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This report was prepared for EPA use and is based on two documents published by the NATO/CCMS Pilot Study on International Information Exchange on Dioxins and Related Compounds. This EPA report summarizes the methodology/rationale used to develop the updated International Toxicity Equivalency Factor/89 (I-TEF/89) method. This EPA report also highlights the changes made from the previous EPA-TEF/87 scheme and the toxicological data supporting those changes.

The contributors to the two NATO/CCMS documents are acknowledged below and represent members of a special "TEF Subgroup" established by the Pilot Study to develop international consensus on a TEF scheme. In addition to the authors and members of the NATO/CCMS Pilot Study, other reviewers of the two NATO/CCMS documents are acknowledged for their contributions to the development of the I-TEF/89 method and the documents describing it.

NATO/CCMS Report 176—International Toxicity Equivalency Factor (I-TEF) Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds

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List of Acronyms

AHH	aryl hydrocarbon hydroxylase
CDDs/CDFs	chlorinated dibenzo-*p*-dioxins and -dibenzofurans
CDWG	Chlorinated Dioxins Work Group
CEC	Commission of the European Communities
EPA	U.S. Environmental Protection Agency
EPA-TEFs/87	toxicity equivalency factors adopted by EPA in 1987 and published ("purple book") as U.S. EPA, 1987
EPA-TEQs/87	toxicity equivalents (based on EPA-TEFs/87)
HxCDD	hexachlorinated dibenzo-*p*-dioxin
HxCDF	hexachlorinated dibenzofuran
HpCDD	heptachlorinated dibenzo-*p*-dioxin
HpCDF	heptachlorinated dibenzofuran
I-TEFs/89	International Toxicity Equivalency Factors adopted by the North Atlantic Treaty Organization - Committee on the Challenges of Modern Society, Pilot Study on International Information Exchange on Dioxins and Related Compounds
I-TEQs/89	International Toxicity Equivalents (based on I-TEFs/89)
MWC	municipal waste combustor
NATO/CCMS	North Atlantic Treaty Organization/Committee on the Challenges of Modern Society, Pilot Study on International Information Exchange on Dioxins and Related Compounds
OCDD	octachlorodibenzo-*p*-dioxin
OCDF	octachlorodibenzofuran
OECD	Organization for Economic Cooperation and Development
PeCDD	pentachlorinated dibenzo-*p*-dioxin
PeCDF	pentachlorinated dibenzofuran
PCP	pentachlorophenol
RfD	reference dose
SAB	EPA's Science Advisory Board
SAR	structure-activity relationship
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	toxicity equivalency factor
TEQ	toxicity equivalents
UNEP	United Nations Environmental Programme
WHO	World Health Organization

I. Overview

In the spring of 1987 the U.S. Environmental Protection Agency (EPA) formally adopted an interim procedure for estimating risks associated with exposures to mixtures of the 210 chlorinated dibenzo-*p*-dioxin and chlorinated dibenzofuran (CDD/CDF) congeners, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) (U.S. EPA, 1987). The procedure, based upon data available through 1985, uses a set of derived toxicity equivalency factors (TEFs) to convert the concentration of any CDD/CDF congener into an equivalent concentration of 2,3,7,8-TCDD. The approach simplifies the assessment of both carcinogenic and noncarcinogenic risks involving exposures to mixtures of CDDs/CDFs.

In the 1987 report, the Agency committed itself to periodically update the TEFs, hereafter referred to as "EPA-TEFs/87." Since 1985, additional data have become available that suggest that modifications in some of the factors are appropriate at this time. In addition, the Agency was active in an international effort aimed at adopting a common set of TEFs ("International TEFs/89" or "I-TEFs/89"), so that information can be exchanged more readily and greater harmony can be achieved in reacting to environmental contamination by CDDs/CDFs. The international project was conducted under the auspices of the North Atlantic Treaty Organization's Committee on Challenges of Modern Society (NATO/CCMS) and benefited from participation by U.S. scientists from both industry and environmental groups, as well as from the EPA.

This first updating report describes the I-TEFs/89, which replace the EPA-TEFs/87 currently in use. This revision is based on an examination of the relevant scientific evidence and a recognition of the value of international consistency in the field.

Section II reviews the development of the original EPA-TEFs/87, the more recent scientific data, and the international activities that have led to the current modifications recommended in the report. Section III focuses on the differences between the EPA-TEFs/87 and I-TEFs/89 and identifies areas where further changes might occur as more data are collected. Section IV provides a concluding summary.

The I-TEFs/89 represent an improvement in an already useful risk assessment tool. However, the approach remains "interim" in character and should be replaced as soon as practicable with a bioassay method, as mentioned in the initial report. Promising progress is being made in this area.

Further, regulatory authorities are encouraged to collect congener-specific data on all CDD/CDF-containing environmental samples and to summarize the estimated combined effect of these chemicals in terms of "International Toxicity Equivalents/89 (I-TEQs/89)." The I-TEQs/89 are obtained by applying the I-TEFs to the congener-specific data and summing the results. Each statement of I-TEQs/89 in a sample should be accompanied by an indication of the percent of those I-TEQs/89 that are contributed by 2,3,7,8-TCDD itself. The congener-specific data will be indispensable in evaluating data in terms of any modified TEF schemes that might appear in the future. In addition, such data might prove helpful in identifying the possible source(s) of CDD/CDF contamination by applying pattern-recognition

techniques to "fingerprints" of congener distributions found in environmental and source samples.

This report is not intended to be a full exposition of the TEF concept and status. Rather, it serves as an update to EPA's initial report (U.S. EPA, 1987) in which the procedure is described in greater detail. In addition, this report builds upon the work of the NATO/CCMS Pilot Study on the International Information Exchange on Dioxins and Related Compounds, whose reports provide further information on the I-TEFs/89 (NATO/CCMS, 1988a,b).

II. Background

A. The TEF Concept

Chlorinated dibenzo-*p*-dioxins and dibenzofurans (CDDs/CDFs) constitute a family of 210 structurally related chemical compounds (Table 1 and Figure 1). During the late 1970s and early 1980s, EPA encountered a number of incidents of environmental pollution in which the toxic potential of CDDs and CDFs figured prominently, e.g., emissions from combustion sources. Initially, concern was focused solely on 2,3,7,8-TCDD, which was produced as a low level by-product during the manufacture of certain herbicides.

Table 1. Number of Congeners by Homologue (number of chlorines) and Substitution Type ("2378" vs. "non-2378")

Type/Homologue	*1Cl*	*2Cl*	*3Cl*	*4Cl*	*5Cl*	*6Cl*	*7Cl*	*8Cl*	*Total*
2378-CDDs	*0*	*0*	*0*	*1*	*1*	*3*	*1*	*1*	*7*
non-2378-CDDs	*2*	*10*	*14*	*21*	*13*	*7*	*1*	*0*	*68*
							Subtotal		*75*
2378-CDFs	*0*	*0*	*0*	*1*	*2*	*4*	*2*	*1*	*10*
non-2378-CDFs	*4*	*16*	*28*	*37*	*26*	*12*	*2*	*0*	*125*
							Subtotal		*135*
								Total 2378-CDDs/Fs	*= 17*
								Total non-2378-CDDs/Fs	*= 193*

Reference: NATO/CCMS, 1988b.

During the past 20 years, many studies have been conducted to elucidate the toxic effects of 2,3,7,8-TCDD. The data obtained from these studies are summarized in a number of reviews (WHO, 1988; NRCC, 1981; Exner, 1987; U.S. EPA, 1985; U.S. EPA, 1988). While these data have not answered all of the questions, the data do show that 2,3,7,8-TCDD can produce a variety of toxic effects, including cancer and reproductive effects, in laboratory animals at very low doses. While some reports in the literature suggest that the chemical can produce similar effects in humans, more definitive information should be forthcoming from epidemiological studies currently in progress (Fingerhut et al., 1989; AOWG, 1987).

For risk assessment purposes, EPA classifies 2,3,7,8-TCDD as a "B2" carcinogen with a potency of 1.6×10^5 $(mg/kg\text{-}d)^{-1}$, by far the most potent carcinogen yet evaluated by the Agency (U.S. EPA, 1985). The chemical is also the most potent reproductive toxin yet evaluated by the Agency, with a Reference Dose (RfD) of 1 pg/kg-d (U.S. EPA, 1985).

More recently, the Agency has confronted a wide variety of cases in which the concentrations of some of the other 209 CDDs/CDFs greatly exceed that of 2,3,7,8-TCDD, e.g., exposure to CDD/CDF impurities in technical pentachlorophenol and CDD/CDF emissions from certain combustion

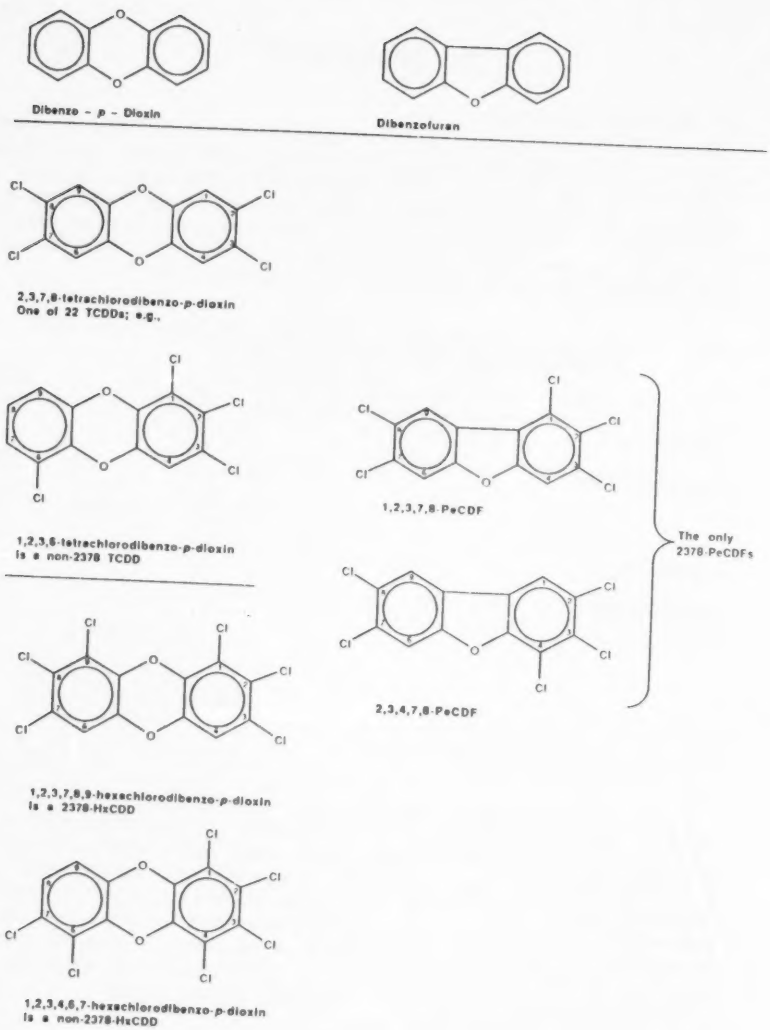


Figure 1. Examples of 2378 and non-2378–substituted dioxins and furans.

sources. Much less is known about the toxicity of these other congeners; however, available information shows cause for some concern. Of the limited number of CDDs/CDFs tested thus far, only a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (HxCDD) has been shown to be carcinogenic in laboratory animals when administered at low doses for a lifetime.

While data available from long-term *in vivo* studies are limited for the majority of CDDs/CDFs, a much larger body of data is available on short-term *in vivo* studies and a variety of *in vitro* studies. These experiments cover a wide variety of end points; e.g., developmental toxicity, cell transformation, and enzyme induction (aryl hydrocarbon hydroxylase [AHH]) (U.S. EPA 1987). While the doses necessary to elicit the toxic response differ in each case, the *relative potency* of the different compounds (compared to 2,3,7,8-TCDD) is generally consistent from one end point to another. This general consistency of relative potency for the same compounds across several end points gives added credence to the TEF concept as it is applied to CDDs/CDFs.

This information, developed by researchers in several labs around the world, reveals a strong structure-activity relationship (SAR) between the chemical structure of a particular CDD/CDF congener and its ability to elicit a biological/toxic response in various *in vivo* and *in vitro* test systems (Bandiera et al., 1984; Olson et al., 1989; U.S. EPA 1987; NATO/CCMS, 1988a,b). Research has also revealed a mechanistic basis for these observations. That is, a necessary (but not sufficient) condition for expression of much of the toxicity of a given CDD/CDF congener is its ability to bind with great specificity to a particular protein receptor located in the cytoplasm of the cell. This congener receptor complex then migrates to the nucleus of the cell, where it initiates reactions leading to expression of toxicity (Poland and Knutson, 1982).

The structure-activity relationship can be summarized as follows: congeners in which the 2, 3, 7, and 8 lateral positions are occupied with chlorines (the so-called "2378-substituted congeners") are much more active than are the other congeners (the so-called "non-2378-substituted congeners") (Figure 1 and Table 1). In addition, when researchers compared the results from a wide variety of studies (both *in vivo* and *in vitro*) for different responses, the relative responses between that of different CDDs/CDFs and that of 2,3,7,8-TCDD were remarkably consistent (Bellin and Barnes, 1983, U.S. EPA 1987).

These observations suggested two important possibilities:

1. The relatively abundant short-term *in vitro* toxicity studies for CDDs/CDFs could be used to supplement (with appropriate caveats) the comparative lack of long-term *in vivo* results for these compounds.
2. An estimate of the long-term *in vivo* toxicities of many of the CDDs/CDFs could be expressed in terms of an equivalent amount of 2,3,7,8-TCDD or "toxicity equivalents" (TEQs). The TEQs could be generated by using a factor (the "toxicity equivalency factor" [TEF]), derived from an examination of the available toxicity data, to convert the concentration of a given CDD/CDF into an equivalent concentration of 2,3,7,8-TCDD.

B. Development of the EPA-TEFs/87

The TEF approach, first suggested in 1977 (Grant, 1977), was pursued by several scientists and jurisdictions during the early- and mid-1980s (e.g., Ontario Government, 1982; Eadon et al., 1986; Swiss Government, 1982; Commoner et al., 1984; California Air Resources Board, 1986). In the early 1980s the Agency's Chlorinated Dioxins Work Group (CDWG) began the development of a TEF scheme to address some of the CDD/CDF problems being encountered by the Work Group. In 1985 the CDWG's parent group, the Dioxin Management Task Force, formally asked the Agency's Risk Assessment Forum (Forum) to review the proposal. During the same time period, the approach was presented at the Fifth International Symposium on Chlorinated Dioxins and Related Compounds and it subsequently appeared in a peer-reviewed journal (Barnes et al., 1986).

The Forum modified the document, principally by making more explicit the process by which the EPA-TEFs/87 were selected. In 1986, the Forum transmitted the document to the Risk Assessment Council (Council) for its review and examination for policy implications. The Council approved the use of the procedure and, in a transmittal memorandum to the Administrator, identified the program areas that were most likely to be impacted by the adoption of the approach. In addition, the Agency's Science Advisory Board (SAB) reviewed the document and, with certain caveats, approved the approach. In January 1987, upon completion of these reviews, the Administrator formally made the EPA-TEF/87 procedure a part of official Agency policy. The interim procedure subsequently appeared as a Forum monograph in March 1987 (U.S. EPA 1987).

Throughout the review process, it was continually emphasized that the TEF approach constituted an *interim* procedure. First, the document explicitly stated that additional research should be conducted to *replace* the EPA-TEF/87 procedure with a preferred approach; i.e., one that directly measures the biological/toxicological response of the mixture of CDDs/CDFs in question. Second, an explicit commitment was made to update the EPA-TEFs/87 themselves as new scientific information dictated.

C. Subsequent Developments on the International Front

During the early 1980s the issue of CDDs/CDFs attracted growing interest in many countries around the world. In fact, several areas of concern about CDDs/CDFs were first noted outside the United States; e.g., the widespread environmental release of 2,3,7,8-TCDD in Seveso, Italy, in 1976 and the European discoveries of the formation of CDDs/CDFs in certain combustion processes in the mid-1970s. During that time, regulatory agencies in the United States (California and New York), Canada, and Europe developed their own TEF schemes. As a result, numerous environmental regulations and statutes were developed which set limits for CDDs and CDFs based on these TEF schemes (NATO/CCMS, 1988c). While the legitimacy of the TEF approach was thereby acknowledged, the existence of so many slightly different TEF schemes complicated communication among scientists and agencies in discussing the toxicological significance of environmental mixtures of CDDs and CDFs. This situation also reflected a lack of any coordinated attempt to reach a scientific consensus on a specific set of TEFs.

In an attempt to provide a forum in which the scientific aspects of these issues could be collegially discussed, the EPA, in conjunction with authorities in the Federal Republic of Germany and in Italy, formed a special "Dioxin Information Exchange" committee under the NATO/CCMS mechanism. The

Pilot Study on International Information Exchange on Dioxins and Related Compounds was initiated in 1985 and focused its attention on the exchange of information on research, exposure/risk assessment, regulation, technology assessment, and management of accidents involving dioxins and related compounds. Other participating nations included Canada, Denmark, the Netherlands, Norway, and the United Kingdom, with Sweden and Austria involved as observer nations. International organizations that were involved included the World Health Organization (WHO), the Commission of the European Communities (CEC), the Organization for Economic Cooperation and Development (OECD), and the United Nations Environmental Programme (UNEP).

In September 1986, in Las Vegas, Nevada, the NATO/CCMS committee formed a subgroup to examine the issues associated with the TEF approach. Specifically, the TEF Subgroup was given the responsibility of developing a position paper on the subject, including:

1. A consensus statement on the appropriateness of the TEF approach; its level of accuracy; its application to both congener-specific and homologue-specific data; and additional research needed to support and even replace the TEF approach.
2. The possibility of reaching an international consensus on a specific set (or range) of TEFs to be applied to CDD/CDF-contaminated environmental samples.
3. The development of consistency within the broad scientific community.

The complete text of the charge to the subgroup can be found in the Appendix.

After one year the TEF Subgroup had made sufficient progress that it was encouraged to seek consensus on a single set of TEFs that could serve the entire international community. Use of a single set of TEFs would increase consistency in data reporting and provide some measure of comparability in risk assessments undertaken around the world. Using previous schemes as a starting point, including a recent one adopted by the Nordic countries (Van Zorge, 1988), the Subgroup developed a specific set of TEFs, dubbed the "International TEFs/89" (I-TEFs/89), for consideration by the parent group. The Subgroup selected the specific TEFs based on available data (U.S. EPA 1987; Olson et al., 1989; NATO/CCMS 1988b) and were guided by the following principles:

1. The scheme should be as simple as practicable. A complex scheme suggests greater precision and sophistication than can be scientifically supported.
2. The focus should be on the CDD and CDF congeners that are preferentially accumulated in mammalian tissue. These are principally the congeners that are substituted at the 2,3,7, and 8 positions and which are the more toxic forms.
3. The TEFs should reflect the relative toxicity exhibited by the various congeners in a variety of toxicological end points.

A draft document describing the I-TEFs/89 was examined and discussed by the participants of the NATO/CCMS Dioxin Information Exchange Committee at its meeting in Berlin in April 1988. After considerable discussion the I-TEFs/89 were approved in principle. The I-TEFs/89 were subsequently published in August 1988 (NATO/CCMS, 1988a) and presented at the Eighth International Symposium on Chlorinated Dioxins and Related Compounds in Umea, Sweden, in August 1988.

The TEF Subgroup was charged with developing a more detailed technical support document, which has now been completed (NATO/CCMS, 1988b). The Dioxin Information Exchange Committee asked the representatives of the member countries to seek formal adoption of the I-TEF/89 scheme by their respective regulatory authorities. This request to seek adoption of the I-TEF/89 scheme comes at a time when the Agency is fulfilling its commitment to periodically update the EPA-TEFs/87, based upon the generation of new information. Several other regulatory agencies in the Nordic countries, the Netherlands, Canada, the United Kingdom, New York State, and Ontario (Canada) have adopted the I-TEF/89 scheme as the preferred interim approach.

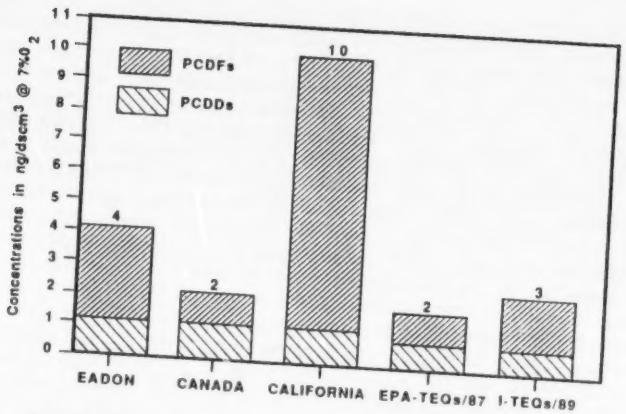
D. Status of the TEF Concept

Events since 1987 clearly indicate that the TEF concept has been widely accepted and used by the scientific and regulatory communities in many parts of the world. Austria, Canada, Denmark, the Federal Republic of Germany, Finland, Italy, the Netherlands, Norway, Sweden, Switzerland, and, the United Kingdom have all moved forward in this area. Japan is considering the approach as well.

Several of these groups have been forthright in citing shortcomings in the science base supporting the TEF concept. Both the NATO report (NATO/CCMS, 1988a) and the World Health Organization report (WHO, 1988) identified limitations to the TEF approach; e.g., the extrapolation from short-term to long-term effects and the possible differences in metabolic effects among species. For example, many of the short-term results seen in murine systems are not observed in rat systems. Also, the connection between the enzyme induction response, which supports several of the TEF values, and several of the toxic end points manifested by CDDs/CDFs, is unclear. Other mechanisms of action, e.g., effect on vitamin A synthesis and estrogen-like activity, have been suggested as playing an important role in the toxicity of CDDs/CDFs.

These continuing elements of uncertainty in the TEF approach highlight the need to treat the approach as "interim," that is, one that needs to be further buttressed by experimental data and eventually replaced with a more direct biological assay. In spite of these acknowledged limitations, all of the groups listed above have endorsed the TEF approach as a feasible procedure for addressing a difficult environmental health problem at this time. Within EPA, the EPA-TEFs/87 have been used effectively by most of the regulatory program offices and many of the Regions. It has been useful to both risk assessors and risk managers in summarizing and communicating the significance of analytical findings of CDDs/CDFs detected in various environmental samples.

During the past two years, however, new toxicological data have been generated that call into question some of the EPA-TEF/87 values assigned to certain of the CDD/CDF congeners (see Section III). (These changes are independent of any recommended changes in the estimated carcinogenic potency of 2,3,7,8-TCDD [U.S. EPA, 1988].) This paper recommends modifications to some of the EPA-TEFs/87 in light of these new data. The effect of these modifications is likely to be modest for many complex mixtures of CDDs and CDFs found in environmental samples, as illustrated by the marginal difference in TEQs calculated by applying the EPA-TEFs/87 and the I-TEFs/89 to data on CDDs/CDFs in emissions from a municipal waste combustor (Figure 2). For mixtures in which 2,3,7,8-substituted congeners



Data for Above Figure (Concentrations in ng/dscm ^{3} @ 7% 0_2)

SPECIES	SOURCE DATA	TEF SCHEME				
		EADON	CANADA	CALIFORNIA	EPA-TEF/87	I-TEF/89
2378-TCDD	0.30	0.30	0.30	0.30	0.30	0.30
TCDDs (OTHER)	2.7	0	0.27	0	0.027	0
12378-PeCDD	0.79	0.79	0.39	0.79	0.39	0.39
PeCDDs (OTHER)	2.2	0	0.011	0	0.011	0
123478-HxCDD	0.16	0.0047	0.016	0.0047	0.0063	0.016
123678-HxCDD	0.39	0.012	0.039	0.012	0.015	0.039
123789-HxCDD	0.059	0.0018	0.0059	0.0018	0.0023	0.0059
HxCDDs (OTHER)	3.6	0	0.0036	0	0.0014	0
1234678-HpCDD	0	0	0	0	0	0
HpCDDs (OTHER)	5.9	0	0.00059	0	0.000059	0
OCDD	9.5	0	0.00095	0	0	0.00095
TOTAL CDDs		1.1	1.0	1.1	0.8	0.8
2378-TCDF	2.3	0.76	0.23	2.3	0.23	0.23
TCDFs (OTHER)	30	0	0.03	0	0.030	0
12378-PeCDF	4.2	1.4	0.42	4.2	0.42	0.21
23478-PeCDF	2.5	0.82	0.25	2.5	0.25	1.2
PeCDFs (OTHER)	12	0	0.012	0	0.012	0
123478-HxCDF	1.6	0.016	0.079	0.047	0.016	0.16
123678-HxCDF	0	0	0	0	0	0
234678-HxCDF	0.46	0.0046	0.023	0.014	0.0046	0.046
123789-HxCDF	0.0095	0.000095	0.00048	0.00029	0.000095	0.00095
HxCDFs (OTHER)	17	0	0.0086	0	0.0017	0
1234678-HpCDF	0	0	0	0	0	0
1234789-HpCDF	0	0	0	0	0	0
HpCDFs (OTHER)	11	0	0.011	0	0.011	0
OCDF	0.41	0	0.000041	0	0	0.00041
TOTAL CDFs		3.0	1.1	9.1	1.0	1.8
TOTAL TEQs		4	2	10	EPA-TEQs/87=2	I-TEQs/89=3
					15% Contributed by 2,3,7,8 - TCDD	10% Contributed by 2,3,7,8 - TCDD

Reference: Adapted from NATO/CCMS, 1988a.

Figure 2. Toxicity equivalents in emissions from a municipal waste incinerator.

predominate (e.g., biological specimens), the I-TEQs/89 will be greater (Figure 3).

In cases in which 2,3,4,7,8-PeCDF, HpCDDs/Fs, and/or OCDD/F predominate, however, the I-TEQs/89 can differ markedly from the EPA-TEFs/87. For example, Figure 4 presents data from soil samples taken from around a pentachlorophenol (PCP) wood treatment site in Region III. The preponderance of hepta- and octa- congeners results in more than an order of magnitude increase in the TEQs estimated by the I-TEF/89 approach compared to the EPA-TEF/87 approach. This is a reflection of the increased weight given to 2378-HpCDDs/Fs and OCDD/F in the I-TEF/89 scheme.

The reader should note, however, that these estimates ignore the issue of relative bioavailability of the CDD/CDF congeners, which have not been thoroughly investigated. Lower relative bioavailability of the hepta- and octa- forms compared to the tetra- forms would generally reduce the concern for TEQ estimates for samples such as those which are dominated by the hepta- and octa- forms. Research in this area is needed to resolve this point.

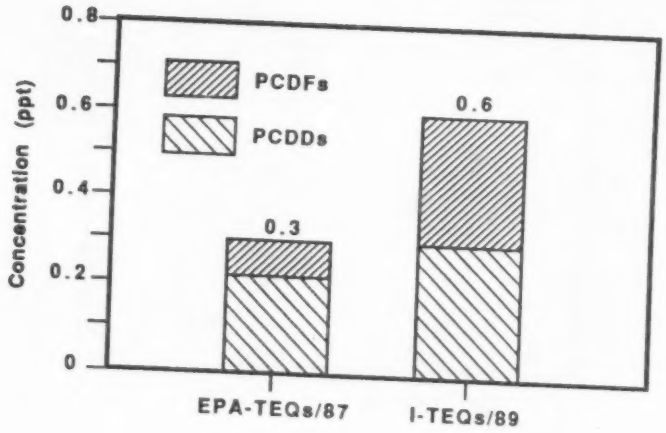
In samples taken from biological organisms exposed to PCP-contaminated soils in Region IX, the TEQs were within a factor of two of each other, when calculated by the I-TEF/89 method or the EPA-TEF/87 method. Although the data are limited, they appear to suggest that the differences in TEQs observed in the PCP-contaminated soil samples are not observed in tissues of organisms exposed to this soil.

The need for additional research remains. This report reiterates the strong recommendation, stated in the 1987 EPA report, that research should continue and primarily focus on developing test methods which can determine more directly and more accurately (and probably less expensively) the biological/toxicological response of complex environmental mixtures of CDDs and CDFs, thereby obviating the need for any TEF scheme. Considerable progress has been made in this area during the past two years (NATO/CCMS, 1988b) and replacement of the TEF approach within the next five years appears to be an achievable goal.

Further, regulatory authorities are encouraged to collect congener-specific data on all CDD/CDF-containing environmental samples and to summarize the estimated combined effect of these chemicals in terms of I-TEQs/89. The I-TEQs/89 are obtained by applying the I-TEFs/89 to the congener-specific data and summing the results. Each statement of I-TEQs/89 in a sample should be accompanied by an indication of the percent of those I-TEQs/89 that are contributed by 2,3,7,8-TCDD itself. The congener-specific data will be indispensable in evaluating data in terms of any modified TEF schemes that might appear in the future. Further, such data might prove helpful in identifying the possible sources(s) of CDD/CDF contamination by applying pattern-recognition techniques to "fingerprints" of congener distributions found in environmental and source samples.

Additional research that would bolster our understanding of this area includes:

1. Exploration of the details of the CDD/CDF-receptor-mediated mechanism of toxicity; e.g., the role of different species/tissue concentrations of the receptor, the intranuclear events leading to enzyme induction, and the marked differences in the responses of different species. Such information may prove useful in understanding other receptor-mediated responses induced by other compounds.
2. Investigation of the link between short-term toxicity (e.g., enzyme induction and subchronic effects) and carcinogenicity and other long-term effects.

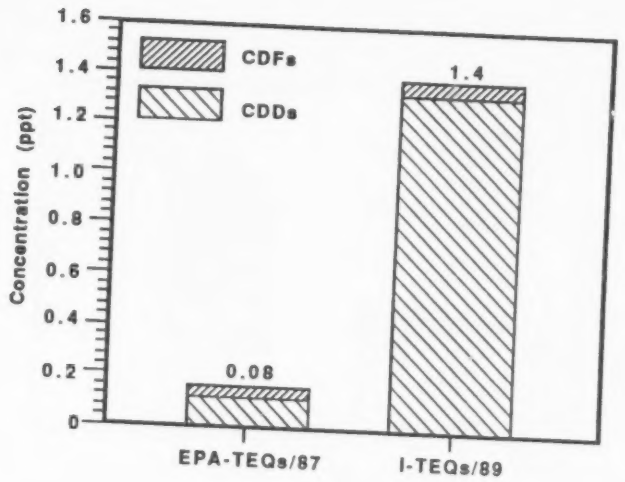


Data for Above Figure:

CONGENER	SOURCE DATA (ppt)	TEF SCHEME	
		EPA-TEF/87	I-TEF/89
2378 - TCDD	0.11	0.11	0.11
12378 - PeCDD	0.18	0.09	0.09
123478 - HxCDD	0.08	0.0032	0.008
123678 - HxCDD	0.73	0.029	0.073
123789 - HxCDD	0.15	0.006	0.015
1234678 - HpCDD	1.3	0.0013	0.013
OCDD	5.7	0	0.0057
TOTAL CDDs		0.24	0.31
2378 - TCDF	0.12	0.012	0.012
12378 - PeCDF	0.022	0.0022	0.0011
23478 - PeCDF	0.51	0.051	0.26
123478 - HxCDF	0.097	0.00097	0.0097
123678 - HxCDF	0.078	0.00078	0.0078
234678 - HxCDF	0.04	0.0004	0.004
1234678 - HpCDF	0.19	0.00019	0.0019
OCDF	0.052	0	0.000052
TOTAL CDFs		0.068	0.30
TOTAL TEQs		EPA-TEQs/87=0.3	I-TEQs/89=0.6
		37% Contributed by 2,3,7,8 - TCDD	18% Contributed by 2,3,7,8 - TCDD

Reference: Lindstrom and Rappe, 1988.

Figure 3. Toxicity equivalents in human milk sample.



Data for Above Figure:

SPECIES	SOURCE DATA (ppt)	TEF SCHEME	
		EPA-TEF/87	I-TEF/89
2378 - TCDD	-	-	-
Other TCDDs	-	-	-
2378 - PeCDD	-	-	-
Other PeCDDs	-	-	-
2378 - HxCDDs	-	-	-
Other HxCDDs	26	0.01	0
2378 - HpCDD	66.4	0.066	0.66
Other HpCDDs	393	0.0039	0
OCDD	678	0	0.68
TOTAL CDDs		0.079	1.34
2378 - TCDF	-	-	-
Other TCDFs	-	-	-
12378 - PeCDF	-	-	-
23478 - PeCDF	-	-	-
Other PeCDFs	-	-	-
2378 - HxCDFs	-	-	-
Other HxCDFs	3.7	0.00037	0
2378 - HpCDFs	3.3	0.0033	0.033
Other HpCDFs	16	0.00016	0
OCDF	41.5	0	0.042
TOTAL CDFs		0.003	0.08
TOTAL TEQs		EPA-TEQs/87=0.08	I-TEQs/89=1.4

Reference: Smith, 1989.

Figure 4. Toxicity equivalents in a pentachlorophenol wood treatment site soil sample.

III. Update of EPA-TEFs/87: Adopting the I-TEF/89 Scheme

A. Similarities Between I-TEFs/89 and EPA-TEFs/87

Table 2 displays the I-TEFs/89 and the EPA-TEFs/87.

The two sets of TEFs have several concepts in common. They share the conceptual framework of the TEF approach. That is, the structure-activity relationship is assumed to be sufficiently strong that estimates of the long-term toxicity of minimally tested congeners of CDDs/CDFs can be reasonably inferred on the basis of available information.

Table 2. Toxicity Equivalency Factors

Compound	EPA-TEFs/87	I-TEFs/89
Mono-, Di-, and TriCDDs	0	0
2,3,7,8-TCDD	1	1
Other TCDDs	0.01	0
2,3,7,8-PeCDD	0.5	0.5
Other PeCDDs	0.005	0
2378-HxCDDs	0.04	0.1
Other HxCDDs	0.0004	0
2,3,7,8-HpCDD	0.001	0.01
Other HpCDDs	0.00001	0
OCDD	0	0.001
Mono-, Di-, and TriCDFs	0	0
2,3,7,8-TCDF	0.1	0.1
Other TCDFs	0.001	0
1,2,3,7,8-PeCDF	0.1	0.05
2,3,4,7,8-PeCDF	0.1	0.5
Other PeCDFs	0.001	0
2378-HxCDFs	0.01	0.1
Other HxCDFs	0.0001	0
2378-HpCDFs	0.001	0.01
Other HpCDFs	0.00001	0
OCDF	0	0.001

Reference: Adapted from NATO/CCMS, 1988a.

In assigning TEFs, priority is generally given to the results from long-term, whole-animal studies followed by the results from short-term, whole-animal studies. Among the remaining short-term *in vivo* and *in vitro* data, priority is generally given to the results of enzyme induction studies. This is due to the

fact that a good correlation has been generally observed between enzyme induction activity and short-term, whole-animal results; i.e., thymic atrophy ($r = 0.91$), body weight loss ($r = 0.84$) in rats, and inhibition of body weight gain in guinea pigs ($r = 0.93$) (NATO/CCMS, 1988b).

The two schemes also share the guiding principle that the TEFs should be as simple as practical, generally expressing TEFs as orders of magnitude. In addition to the operational simplicity involved, this principle is meant to reflect the fact that the TEFs are only crude approximations of relative toxicities.

In addition, similarities in the two methods are also reflected in the fact that the toxicities of mono- through tri-substituted compounds are considered to be negligible, and the TEFs are interim estimates that can and should be altered in light of new information.

B. Differences Between I-TEFs/89 and EPA-TEFs/87

1. *Increased Simplicity*

The numerous TEF schemes that have been generated over the past few years differ by relatively small amounts. Aside from a scheme originally introduced by one of the states and since altered, the range of TEQs resulting from the application of the different schemes to the same environmental sample generally spans a range of less than fivefold. Consequently, small changes in TEFs (U.S. EPA, 1987) and identification of a different number of the "congeners of concern" (e.g., the 12 versus 15 toxic congeners [Rappe et al., 1987 versus U.S. EPA, 1987]) suggest refinements in precision, accuracy, and impact that are not reflected in the actual results. Therefore, the I-TEF/89 scheme has reduced the total number of congeners considered and, with the exception of the PeCDFs, has expressed the TEFs as a round order of magnitude.

The guiding principle of simplicity is further reflected in the specific differences noted below.

2. *I-TEFs/89 for all Non-2378 Congeners are Zero*

The I-TEF/89 approach assigns a value of zero to non-2378-substituted congeners. In the EPA-TEF/87 scheme, the TEFs for non-2378-substituted congeners were assigned values that were 1% of the TEFs for the 2378-substituted congeners in the same homologous group. For example, in the EPA-TEF/87 scheme, 1,2,3,7,8-PeCDD was assigned a value of 0.5 and the other 13 non-2378 PeCDDs were assigned a value of 0.005. In the I-TEF/89 scheme, 1,2,3,7,8-PeCDD retains its TEF of 0.5, but the 13 other PeCDDs are assigned a value of zero.

Rationale:

During the past two years, scientists have gathered additional data indicating that nearly all of the 210 CDDs/CDFs can be found at very low levels in many parts of the environment. However, it appears that the 2378-substituted congeners are selectively absorbed and/or retained in higher animals; e.g., fish, humans, and other mammals. That is, of the CDDs/CDFs detected in a variety of tissues from these sources, the 2378-substituted CDD/CDF congeners clearly predominate over the non-2378-substituted congeners. This is true even when the source of the CDDs/CDFs is relatively low in the concentration of 2378-substituted congeners.

For example, fly ash from municipal waste combustors (MWCs) generally contains detectable amounts of CDDs/CDFs. In most instances, the amount of non-2378-substituted congeners vastly outweighs the amount of 2378-substituted congeners in such samples. However, when mice or fish are exposed to MWC fly ash and their tissues are subsequently analyzed for the presence of CDDs/CDFs, essentially *only* the 2378-substituted congeners are detected (Kuehl et al., 1986; Van den Berg et al., 1985). Similarly, the "background levels" of CDDs/CDFs routinely found in human tissues (fat, blood, and milk) contain almost exclusively 2378-substituted congeners (Rappe et al., 1987).

The environmental concern of the Agency rests primarily with long-term exposures. It is the 2378-substituted congeners that seem to pose the greatest long-term potential, since the non-2378-substituted congeners appear to be either not absorbed or quickly eliminated by biological systems. Therefore, in the interest of keeping the TEF system as simple as possible, attention is focused exclusively on 2378-substituted congeners in the I-TEF/89 scheme.

3. *Distinguishing Between 1,2,3,7,8- and 2,3,4,7,8-PeCDF*

For the homologous class of 2378-substituted PeCDFs, the I-TEF/89 scheme introduces an additional complexity that was not a part of the EPA-TEF/87 scheme. In the EPA-TEF/87 scheme, both isomers were assigned a value of 0.1. In the I-TEF/89 scheme, the 2,3,4,7,8-PeCDF is assigned a value of 0.5, while the 1,2,3,7,8-PeCDF is assigned a value of 0.05. This is the only instance in which the I-TEFs/89 depart from the guiding principle of "simplicity" in which TEFs are expressed as rounded orders of magnitude. This departure is prompted by a growing body of data that indicate that 2,3,4,7,8-PeCDF is notably more active than originally thought.

Rationale:

Based upon the data in Table 3, it can be seen that:

(a) The 0.5 value for 2,3,4,7,8-PeCDF gains support from the *in vivo* thymic atrophy data (0.43) and the mouse immunotoxicity data (0.8).

(b) The 0.05 value for 1,2,3,7,8-PeCDF gains support from the *in vivo* investigations of thymic atrophy data (0.05) and the *in vivo* and *in vitro* investigations of enzyme induction data (0.003-0.06).

(c) The higher value for 2,3,4,7,8-PeCDF over 1,2,3,7,8-PeCDF is also supported by mouse teratogenicity data. Note that there is one outlier in the eight data points reported for 1,2,3,7,8-PeCDF in Table 3. Specifically, there is a 0.95 value recorded for reduction in body weight gain seen in guinea pigs. This one experiment in one laboratory should be investigated further to determine its possible significance. At the present time, however, the weight of the evidence argues for the lower TEF.

The fact that the two 2378-substituted congeners can elicit such different biological responses can be rationalized by examining the stereochemistry of the two chemicals (Bandiera et al., 1984). When superimposed on the molecular structure of 2,3,7,8-TCDD, the C-4 of the "bent" PeCDF is more stereochemically a "lateral position" (i.e., closer to C-3 on the 2,3,7,8-TCDD skeleton), while the C-1 is even less stereochemically a "lateral position" (i.e., farther away from C-2) (see Figure 5). Therefore, the 2,3,4,7,8-PeCDF would theoretically be expected to be more active than the 1,2,3,7,8-PeCDF since it has more chlorine substituents in the lateral positions.

Table 3. International Toxicity Equivalency Factors/89 (I-TEFs/89): Comparison of Relative Potency Data for the 2378-Substituted CDDs and CDFs

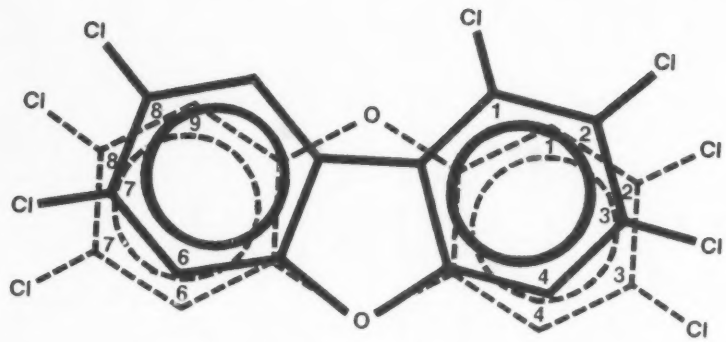
Congener	I-TEFs/89	Observed TEF Ranges			Relevant section in text
		(in vivo toxicities)	Aryl hydrocarbon hydroxylase induction		
			(in vivo)	(in vitro)	
2,3,7,8-TCDD	1	1	1	1	–
1,2,3,7,8-PeCDD	0.5	Range = 0.053-0.59 Data = (0.59[ml], 0.42[gl], 0.081[r], 0.053[r])	0.13 (0.13[r])	Range = 0.0065-0.011 Data = (0.011/0.0065[h])	–
1,2,3,4,7,8-HxCDD	0.1	Range = 0.018-0.24 Data = (0.24[ml], 0.084[r], 0.018[gl], 0.13[r])	0.13 (0.13[r])	Range = 0.034-0.046 Data = (0.034/0.046[h])	III.B.4
1,2,3,7,8,9-HxCDD	0.1	Range = 0.016-0.14 Data = (0.016[gl], 0.14[ml])	–	0.008 (0.008[hB])	III.B.4
1,2,3,6,7,8-HxCDD	0.1	Range = 0.015-0.16 Data = (0.16[ml], 0.015[gl])	–	0.012 (0.012[hB])	III.B.4
1,2,3,4,6,7,8-HpCDD	0.01	–	–	0.003 (0.003[hB])	III.B.4
OCDD	0.001	–	0.0002[c]	0.0006 (0.0006[hB])	III.B.4

Table 3. (continued)

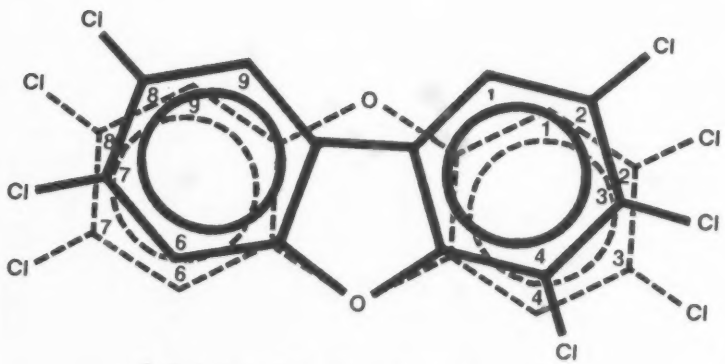
Congener	I-TEFs/89	Observed TEF ranges (in vivo toxicities)	Aryl hydrocarbon hydroxylase induction (in vivo)	Aryl hydrocarbon hydroxylase induction (in vitro)	Relevant section in text
2,3,7,8-TCDF	0.1	Range = 0.16-0.17 Data = (0.017[g], 0.17[mi], 0.05[mt], 0.025[r], 0.016[r])	0.006 (0.006[r])	Range = 0.018-0.09 Data = (0.018/0.09[h])	–
2,3,4,7,8-PeCDF	0.5	Range - 0.048-0.80 Data = (0.8[mi], 0.47[g], 0.43[r], 0.13[g], 0.12[mt], 0.048[r])	0.11-0.23 (0.23[g], 0.11[r])	Range = 0.28-1.41 Data = (0.28-1.41[h])	III.B.3
1,2,3,7,8-PeCDF	0.05	Range = 0.019-0.95 Data = (0.95[g], 0.05[r], 0.031[mt], 0.019[r])	0.003-0.047 (0.047[g], 0.003[r])	Range = 0.028-0.06 Data = (0.06/0.028[h])	III.B.3
1,2,3,4,7,8-HxCDF	0.1	Range = 0.013-0.18 Data = (0.18[r], 0.038[r], 0.013[mt])	0.014 (0.014[r])	Range = 0.20-0.50 Data = (0.20/0.50[h])	III.B.4
1,2,3,6,7,8-HxCDF	0.1	Range = 0.016-0.097 Data = (0.097[r], 0.016[r])	0.012 (0.012[r])	Range = 0.049-0.153 Data = (0.049/0.153[h])	III.B.4
1,2,3,7,8,9-HxCDF	0.1	–	–	–	III.B.4
2,3,4,6,7,8-HxCDF	0.1	Range = 0.011-0.097 Data = (0.097[r], 0.018[r], 0.011[g])	0.015 (0.015[r])	Range = 0.11-0.33 Data = (0.11/0.33[h])	III.B.4
1,2,3,4,6,7,8-HpCDF	0.01	–	–	–	III.B.4
1,2,3,4,7,8,9-HpCDF	0.01	–	–	–	III.B.4
OCDF	0.001	–	–	–	III.B.5

[g]guinea pig and [r]rat data
[gl]guinea pig and [ml]mouse lethalities
[c]Couture et al., 1988
[mt]mouse teratogenicity and [mi]mouse immunotoxicity
[h]rat hepatoma data (AAH/EROD)
[hB]rat hepatoma data (AAH)

Reference: Derived from Tables 3, 4, 5, 7, and 8 from NATO/CCMS, 1988b.



1, 2, 3, 7, 8 - PeCDF on 2, 3, 7, 8 - TCDD



2, 3, 4, 7, 8 - PeCDF on 2, 3, 7, 8 - TCDD

Figure 5. 2378–Substituted pentachlorodibenzofurans (Adapted from Bandiera et al., 1984).

4. *Increasing the TEFs for the 2378-HxCDDs/Fs and -HpCDDs/Fs*

The I-TEF/89 for 2378-HxCDDs is 0.1, compared to 0.04 in the EPA-TEF/87 approach. The I-TEFs/89 for the 2378-substituted HxCDFs and HpCDDs/Fs (0.1 and 0.01, respectively) are tenfold higher than the values in the EPA-TEF/87 scheme.

Rationale:
Different lines of argument support these changes:

2378-HxCDDs

(a) Following the principle of simplicity, a whole order of magnitude number (0.1) is more appropriate than a fractional order of magnitude number (0.04).

(b) As seen in Table 3, the 0.1 value is supported by short-term *in vivo* thymic atrophy (0.084) and aryl hydrocarbon hydroxylase (AHH) induction (0.13) results for 1,2,3,7,8-HxCDD. The *in vitro* enzyme induction results are generally an order of magnitude lower.

(c) Since the presence of non-2378-substituted congeners is effectively ignored in the I-TEF/89 scheme, somewhat higher TEFs for the 2378-congeners tend to compensate for the small toxic contribution of any non-2378 congeners that were explicitly included in the EPA-TEF/87 scheme.

The EPA-TEFs/87 assigned a value of 0.04 to the 2378-HxCDDs, based upon the results of a study by the National Toxicology Program in which a mixture of 2378-HxCDDs was fed to rodents during their lifetimes. It was argued that such *in vivo* data should take precedence over shorter-term and/or *in vitro* data, since the former are generally more relevant to the exposures of concern to humans. In this document, however, the arguments of simplicity and the value of international consensus carry more weight, especially in light of the approximate nature of the results of a single animal study.

2378-HxCDFs

(a) The 0.1 value is supported by short-term *in vivo* thymic atrophy data, i.e., 0.18 and 0.097 for 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF, respectively. The inhibition of weight gain results are about an order of magnitude lower. The *in vitro* enzyme induction results range from 0.05 to 0.2; however, they are given less weight since they are not whole animal studies.

(b) Since the presence of non-2378-substituted congeners is effectively ignored in the I-TEF/89 scheme, somewhat higher TEFs for the 2378-substituted congeners tend to compensate for the small toxic contribution of any non-2378-substituted congeners that were specifically included in the EPA-TEF/87 scheme.

2378-HpCDDs/Fs

(a) The data base is very slim for these compounds. Only short-term *in vitro* data exist. On the surface, these data would argue for a 0.001 value. However, recent whole animal data suggest that the perchlorinated CDDs/CDFs slowly bioaccumulate in exposed organisms (Couture et al., 1988). Highly chlorinated species such as HpCDDs/HpCDFs are likely to behave in a similar fashion. Therefore, an extra measure of prudence is advisable; hence, an I-TEF/89 of 0.01 was chosen.

(b) Since the presence of non-2378-substituted congeners is effectively ignored in the I-TEF/89 scheme, somewhat higher TEFs for the 2378-substituted congeners tend to compensate for the small toxic contribution of any non-2378-substituted congeners that were specifically included in the EPA-TEF/87 scheme.

5. *Assigning Non-Zero TEF Values to OCDD and OCDF*

The I-TEF/89 scheme assigns a value of 0.001 to OCDD and OCDF. The EPA-TEF/87 approach assigned these congeners a value of zero.

Rationale:

In the EPA-TEF/87 scheme, OCDD and OCDF were assigned values of zero on the basis of results of limited short-term *in vivo* and *in vitro* data. In a recently published study (Couture et al., 1988), however, male rats were exposed to low levels of OCDD for 13 weeks. At the end of the experiment, the animals were beginning to show signs of toxicity that were reminiscent of "dioxin toxicity." Detectable levels of OCDD had accumulated in the organism. These data suggest that OCDD exhibits minimal toxicity in short-term studies simply because so little of the compound is absorbed in a short time. Exposed for longer periods, however, the animals appear to absorb and accumulate sufficient amounts of the compound in their systems to manifest "dioxin-like" effects.

Based on these new data (summarized in Table 3), a TEF value of 0.001 has been assigned to both OCDD and OCDF in the I-TEF/89 scheme. It should be noted, however, that this value reflects the results of a single experiment.

IV. Summary

Table 2 shows the EPA-TEFs/87 and the I-TEFs/89. The changes reflect an international consensus reached by a working group of the NATO/CCMS and adopted in principle in April 1988. Adoption of this consensus position by the international scientific and regulatory communities will facilitate communication about and discussion of environmental contamination involving CDDs/CDFs.

The values should continue to be viewed as rough approximations that are "interim" in nature, requiring periodic updating. In addition, there should be a continuation of research into the development of a biologically based analysis that can quickly and accurately measure the toxicological potential of complex mixtures of CDDs and CDFs. Such research holds the promise of removing the need for any TEF scheme. This is particularly important in light of the emerging data showing that some of the CDDs/CDFs and related compounds can exhibit antagonistic effects (Safe, 1987), a possibility that is ignored in current TEF approaches.

There is only a marginal difference between the EPA-TEF/87 and I-TEF/89 schemes when the different factors are applied to the same complex mixture of CDDs/CDFs, such as those found in MWC fly ash or biological samples (Figures 2 and 3). Consequently, small changes away from the international consensus I-TEFs/89 should be discouraged. That is, any arguable increase in accuracy is likely to be small and will be purchased at the cost of a decrease in effective communication and an increase in conflict/confusion among scientists, agencies, and affected members of the public.

The authors would like to strongly reiterate that analytical chemists are encouraged to analyze mixtures on a congener-specific basis, to the extent possible. Such information may prove to be invaluable in identifying sources of and transformation processes for CDDs/CDFs in the environment. In addition, such detailed information will permit recalculation of estimated toxicities for these samples if I-TEF/89 values are changed in the future in light of new scientific data. In any event, summary results should be expressed in I-TEQs/89 with the contribution from 2,3,7,8-TCDD clearly noted (see Figures 2 and 3).

Several matters should receive close scrutiny prior to any future updating of the I-TEF/89 values. For example, a case could be made that the I-TEF/89 for 1,2,3,7,8-PeCDF is too low. However, this suggestion is based upon one experiment whose results are not consistent with the results of several other tests. Additional work should be conducted on this compound to resolve the apparent ambiguity. Also, investigations should be conducted to determine whether compounds in which only three of the four critical lateral positions are occupied merit non-zero values. Finally, more work needs to be done to clarify the toxicity associated with long-term exposures to low levels of highly chlorinated CDDs/CDFs.

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Appendix

Proposal on the Toxicity Equivalency Factor (TEF) Concept to Assessing Risks of CDDs/CDFs September 1986

Given the growing concern about the broad range of CDDs/CDFs reported in a large number of environmental media, various groups have developed toxicity equivalency factors (TEFs) for converting levels of CDDs/CDFs into "equivalent" amounts of 2,3,7,8-TCDD. While these approaches are not defensible on indisputable scientific grounds, there is a generally acknowledged underlying scientific rationale for such a policy position.

As various groups have developed related but somewhat different schemes for TEFs, there has emerged a need for a broad-based international consensus statement on the concept of the TEF approach so that risk managers and the public can properly appreciate these schemes. Therefore, Working Group A on exposure and hazard assessment is forming a subcommittee to address TEFs at two levels:

A. Proposal

1. Level 1

(a) Develop a consensus statement on the appropriateness of the TEF concept.

(b) Develop a consensus statement on the level of accuracy that should be attributed to the TEF concept and any of its specific approaches.

(c) Develop a statement on various ways in which homologue-specific data might be treated under TEF approach(es) and what the impacts of those various treatments might be.

(d) Develop a specific scheme (including cost and time requirements) of research that will lead to the replacement of TEF approach(es) by more firmly based scientific procedures.

2. Level 2

(a) Explore reaching a consensus on a specific set (or range) of TEFs and determining how subsequent updatings in the TEFs might be generated.

(b) Explore incorporating into TEF approach(es) certain aspects of pharmacokinetics.

(c) Explore the feasibility and advisability of having analytical chemists report, in addition to their congener- and/or homologue-specific results, results expressed in terms of one or more TEF approaches.

B. Mechanism

(a) A subcommittee, composed of single representatives from each CCMS member nation interested in the project, will be formed under

the chairmanship of the United States. The names of the designated members are due to Mr. Bretthauer, Group A Chair, by October 25, 1986.

(b) During the next 10 months, the subcommittee will interact to accomplish the tasks in Level 1 and make as much progress as possible on the items in Level 2.

(c) As part of their efforts, and as a platform for airing the issues, the subcommittee will organize a special session on TEF and related topics at Dioxin 1987 meeting in Las Vegas.

(d) The subcommittee will present its results and recommendations at the CCMS meeting next fall for consideration by the full CCMS Committee on Dioxin Information Exchange.

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